

Exhibit A:

1. Copy of executed assignment from inventors Klaus Sommermeyer, Franz Cech, Burghard Weidler, and Klaus Henning to Fresenius Aktiengesellschaft (AKA Fresenius AG), recorded in the United States Patent and Trademark Office on Reel 005345, Frames 0989 through 0992.
2. Copy of executed confirmatory assignment from Fresenius Aktiengesellschaft to Fresenius Kabi Deutschland GmbH (AKA Fresenius Kabi)

ASSIGNMENT

464 01/533234 TR 1024

WHEREAS, We Dr. K. Sommermeyer,  
Dr. F. Cech, Dr. K. Henning and           
Dr. B. Weidler, are the joint inventors of           
        , application for United States Letters Patent  
which is executed of even date herewith; and

WHEREAS, FRESENIUS AG, D-6380 Bad Homburg v.d.H., a  
corporation created and existing under and by virtue of the laws of the  
State and/or Country of the Federal Republik of Germany, is  
desirous of acquiring the entire right, title and interest in and to the  
aforesaid invention throughout the world, and all right, title and  
interest in, to and under any and all Letters Patent of the United States  
and all other countries throughout the world;

NOW, THEREFORE, for and in consideration of the sum of One Dollar  
(\$1.00) to us in hand paid by FRESENIUS AG  
and for other good and valuable considerations, the receipt of which is  
hereby acknowledged, we hereby sell, assign, transfer and set over to  
FRESENIUS AG, all right, title and  
interest in and to the said invention throughout the world, and said  
application for U.S. Letters Patent, and any and all divisions,  
continuations, and reissues thereof, and any and all Letters Patent of  
the United States and foreign countries which may be granted therefor,  
the same to be held and enjoyed by FRESENIUS AG  
         for its own use and benefit, and for the  
use and benefit of its successors, assigns, or other legal  
representatives, to the end of the term or terms for which said Letters  
Patent of the United States or foreign countries are or may be granted or  
reissued, as fully and entirely as the same would have been held and  
enjoyed by us if this assignment and sale had not been made.

And we hereby authorize and request the Commissioner of Patents and  
Trademarks to issue any and all Letters Patent of the United States on  
said invention or resulting from said application and from any and all  
divisions, continuations, and reissues thereof, to FRESENIUS AG

REEL 5345 FRAME 990

\_\_\_\_\_, as assignee of our entire interest, and hereby covenant that we have the full right to convey the entire interest herein assigned, and that we have not executed and will not execute any agreement in conflict herewith.

And we further hereby covenant and agree that we will, at any time, upon request, execute and deliver any and all papers that may be necessary or desirable to perfect the title of said invention and to such Letters Patent as may be granted therefor, to FRESENIUS AG

\_\_\_\_\_, its successors, assigns, or other legal representatives and that if FRESENIUS AG

\_\_\_\_\_, its successors, assigns or other legal representatives shall desire to file any divisional or continuation applications or to secure a reissue of such Letters Patent, or to file a disclaimer relating thereto, will upon request, sign all papers, make all rightful oaths and do all lawful acts requisite for the filing of such divisional or continuation application, or such application for reissue and the procuring thereof, and for the filing of such disclaimer, without further compensation but at the expense of said assignee, its successors, or other legal representatives.

And we do further covenant and agree that we will, at any time upon request, communicate to FRESENIUS AG, its successors, assigns or other legal representatives, such facts relating to said invention and Letters Patent or the file history thereof as may be known to me, and testify as to the same in any interference or other litigation when requested so to do, without further compensation but at the expense of said assignee, its successors, or other legal representatives.

EXECUTED THIS 25 day of April, 1990.

Signature \_\_\_\_\_

Dr. K. Sommermeier

EXECUTED THIS 25 day of April, 1990.

Signature \_\_\_\_\_

Dr. F. Cech

REEL 5345 FRAME 991

EXECUTED THIS 26 day of April, 1990.

Signature X

Dr. B. Weidler

EXECUTED THIS 25 day of April, 1990.

Signature Ula, Henning

Dr. K. Henning

REF 5345 FR 1992

RECORDED  
PATENT AND TRADEMARK  
OFFICE

JUN 5 1990

CONFIRMATORY ASSIGNMENT

Whereas, by virtue of an Assignment recorded in the United States Patent and Trademark Office on Reel 005345, Frames 0989 through 0992, Fresenius Aktiengesellschaft (hereinafter "Assignor") of Else-Kroener-Strasse 1, 61352 Bad Homburg v.d.H., Germany, was the owner of United States Letters Patent No. 5,218,108, issued June 8, 1993 (hereinafter "Patent").

Whereas, Fresenius Kabi Deutschland GmbH (hereinafter "Assignee"), a German corporation, of Else-Kroener-Strasse 1, 61352 Bad Homburg v.d.H., Germany, was desirous of acquiring from Assignor, an interest in, to and under the aforesaid Patent and the invention therein described and claimed, and in accordance with an agreement executed June 9, 1999 (hereinafter "Agreement"), Assignee acquired from Assignor all of its right, title and interest in the Patent in return for certain obligations to Assignor.

Now, therefore, Assignor hereby confirms that for good and valuable consideration, the receipt of which was hereby acknowledged in the Agreement, it has sold, transferred and conveyed to Assignee its entire right, title and interest in, to and under said Patent, to the full end of the term for which Letters Patent were granted, and any continuations, reissues, or extensions thereof and the invention therein described and claimed, including all claims, if any, which may have arisen for infringement of the Patent prior to the date of this confirmatory assignment.

Assignor further agrees that Assignor will, without demanding any further consideration therefor, at the request but at the expense of Assignee, do all lawful and just acts, including the execution and acknowledgment of instruments, that may be or become necessary for obtaining, sustaining, or reissuing the Patent, and for maintaining and perfecting Assignee's right, its

successors, assigns and legal representatives, to the Patent and any continuations, reissues or extensions thereof, and preliminary or other statements and the giving of testimony in any interference or other proceeding in which said invention or any application or patent directed thereto may be involved.

Fresenius Aktiengesellschaft

By B. Staudte

Print Name: I.V. Bright Staudte  
Patent Manager

Title

Date February 18, 2008

Witness Signature S. Calabro - Folchert

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Patent Manager

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35428 Langgöns

Witness Signature [Signature]

Print Witness Name Stefan Weiss

Address Hofackerweg 7

60320 Frankfurt

## NON ANNOTATED VERSION

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Voluven® safely and effectively. See full prescribing information for Voluven®.

**Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection)**

**For administration by intravenous infusion.**

**Initial U.S. Approval: To be determined**

### INDICATIONS AND USAGE

Voluven® is a plasma volume substitute indicated for the treatment and prophylaxis of hypovolemia. (1)

### DOSAGE AND ADMINISTRATION

**Administer by intravenous infusion only.**

- Daily dose and rate of infusion depend on the patient's blood loss, hemodynamics and on the hemodilution effects. (2)
- Initiate infusion slowly due to possible anaphylactoid reactions (2, 5.1)
- See full prescribing information for pediatric administration (2.2, 8.4)

### DOSAGE FORMS AND STRENGTHS

500 mL *freeflex*® flexible plastic intravenous solution container. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection. (3)

### CONTRAINDICATIONS

- Known hypersensitivity to hydroxyethyl starch (4)
- Fluid overload e.g., pulmonary edema and congestive heart failure (4)
- Renal failure with oliguria or anuria not related to hypovolemia (4)
- Patients receiving dialysis (4)
- Severe hyponatremia or severe hyperchloremia (4)
- Intracranial bleeding (4)

### WARNINGS AND PRECAUTIONS

- Anaphylactoid and hypersensitivity reactions (5.1, 6)
- Avoid fluid overload; adjust dosage in patients with cardiac or renal dysfunction (5.1)
- In severe dehydration, a crystalloid solution should be given first (5.1)
- Observe caution in patients with severe liver disease or bleeding disorders (5.1)
- Monitor kidney function, fluid balance and serum electrolytes (5.2)
- Elevated serum amylase values may occur and interfere with the diagnosis of pancreatitis (5.3)
- High dosages may cause dilution of blood components (5.3)

#### **-----ADVERSE REACTIONS-----**

Anaphylactoid/hypersensitivity reactions can occur. Most common adverse reactions (incidence >1%) are pruritus, elevated serum amylase, hemodilution (resulting in dilution of blood components, e.g., coagulation factors and other plasma proteins, and in a decrease in hematocrit). (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Hospira Inc. at 1-800-441-4100 or electronically at ProductComplaintsPP@hospira.com or FDA at 1-800-FDA-1088 or electronically at [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### **-----DRUG INTERACTIONS-----**

No interactions with other drugs or nutritional products are known. (7)  
The safety and compatibility of additives have not been established.

#### **-----USE IN SPECIFIC POPULATIONS-----**

- Pediatric patients: Dosage should be adjusted to individual patient needs. (2.2, 8.4)
- Renal impaired or geriatric patients: Use care in dosage selection. (8.6)

**After reviewing the Highlights section, please read the following full prescribing information for this drug.**

See 17 for PATIENT COUNSELING INFORMATION  
**Labeling Revision Date:** TBD

*Draft: 2007/12/18*

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Voluven<sup>®</sup> (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) is indicated for the treatment and prophylaxis of hypovolemia.

It is not a substitute for red blood cells or coagulation factors in plasma.

### 2 DOSAGE AND ADMINISTRATION

Voluven<sup>®</sup> is administered by intravenous infusion only. The daily dose and rate of infusion depend on the patient's blood loss, on the maintenance or restoration of hemodynamics and on the hemodilution (dilution effect). Voluven<sup>®</sup> can be administered repetitively over several days. [see *Warnings and Precautions* (5)]

The initial 10 to 20 mL should be infused slowly, keeping the patient under close observation due to possible anaphylactoid reactions. [see *General Warnings and Precautions* (5.1)]

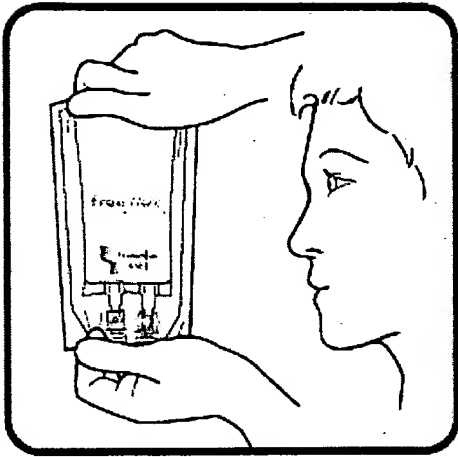
#### 2.1 Adult Dose

Up to 50 mL of Voluven<sup>®</sup> per kg of body weight per day (equivalent to 3 g hydroxyethyl starch and 7.7 mEq sodium per kg of body weight). This dose is equivalent to 3500 mL of Voluven<sup>®</sup> for a 70 kg patient.

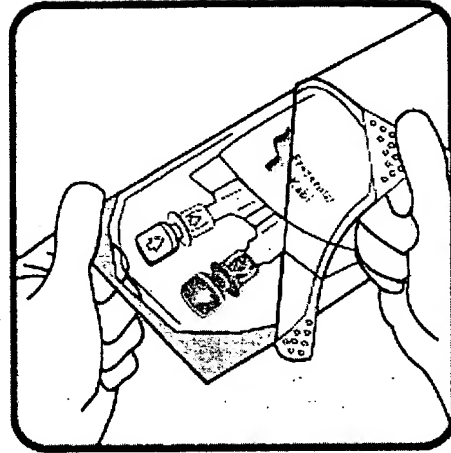
#### 2.2 Pediatric Dose

Limited clinical data on the use of Voluven<sup>®</sup> in children are available. In 41 children including newborns to infants (< 2 years), a mean dose of  $16 \pm 9$  mL/kg was administered. The dosage in children should be adapted to the individual patient colloid needs, taking into account the disease state, as well as the hemodynamic and hydration status. The safety and efficacy of Voluven<sup>®</sup> have not been established in the age group of 2 to 12 years. Use of Voluven<sup>®</sup> in children > 12 years is supported by evidence from adequate and well-controlled studies of Voluven<sup>®</sup> in adults and by data from children < 2 years old. [see *Pediatric Use* (8.4)]

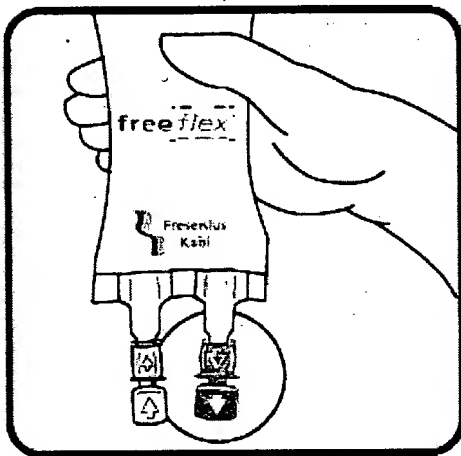
#### 2.3 Directions for Use of Voluven<sup>®</sup>



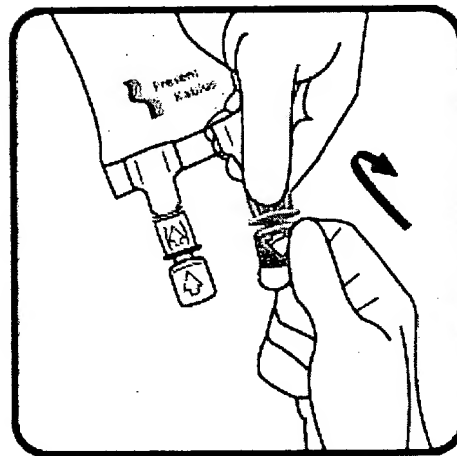
- Check the solution composition, lot number and expiry date, inspect the container for damage or leakage, if damaged do not use.



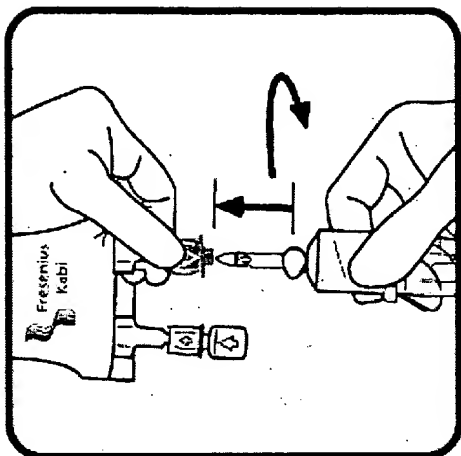
- Use opening aid to remove over-wrap.



- Identify the blue infusion (administration) port.



- Break off the blue tamper-evident cover from the **freeflex**® infusion port.



- Hang the bag on the infusion stand. Press drip chamber to get fluid level. Prime infusion set. Connect and adjust the flow rate.

- Close roller clamp. Insert the spike until the clear plastic collar of the port meets the shoulder of the spike.
  - Use a non-vented standard infusion set and close air inlet.
1. Do not remove the **freeflex**<sup>®</sup> IV container from its overwrap until immediately before use.
  2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
  3. Do not administer unless the solution is clear, free from particles and the **freeflex**<sup>®</sup> IV container is undamaged.
  4. Voluven<sup>®</sup> should be used immediately after insertion of the administration set.
  5. Do not vent.
  6. If administered by pressure infusion, air should be withdrawn or expelled from the bag through the medication/administration port prior to infusion.
  7. Discontinue the infusion if an adverse reaction occurs.
  8. It is recommended that administration sets be changed at least once every 24 hours.
  9. For single use only. Discard unused portion.

### **INCOMPATIBILITIES**

The safety and compatibility of additives have not been established.

### **3 DOSAGE FORMS AND STRENGTHS**

500 mL **freeflex**<sup>®</sup> flexible plastic intravenous solution container are available. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection.

#### **4 CONTRAINDICATIONS**

The use of Voluven® is contraindicated in the following conditions:

- known hypersensitivity to hydroxyethyl starch [see *General Warnings and Precautions (5.1)*]
- fluid overload (hyperhydration) and especially in cases of pulmonary edema and congestive heart failure
- renal failure with oliguria or anuria not related to hypovolemia
- patients receiving dialysis treatment
- severe hyponatremia or severe hyperchloremia
- intracranial bleeding.

#### **5 WARNINGS AND PRECAUTIONS**

##### **5.1 General Warnings and Precautions**

Anaphylactoid reactions (mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema) have been reported with solutions containing hydroxyethyl starch. If a hypersensitivity reaction occurs, administration of the drug should be discontinued immediately and the appropriate treatment and supportive measures should be undertaken until symptoms have resolved. [see *Adverse Reactions (6)*]

Fluid status and rate of infusion should be assessed regularly during treatment, especially in patients with cardiac insufficiency or severe kidney dysfunction.

In cases of severe dehydration, a crystalloid solution should be given first. Generally, sufficient fluid should be administered in order to avoid dehydration.

Caution should be observed before administering Voluven® to patients with severe liver disease or severe bleeding disorders (e.g., severe cases of von Willebrand's disease).

##### **5.2 Monitoring: Laboratory Tests**

Clinical evaluation and periodic laboratory determinations are necessary to monitor fluid balance, electrolyte concentrations, kidney function, acid-base balance, and coagulation parameters during prolonged parenteral therapy or whenever the patient's condition warrants such evaluation.

##### **5.3 Interference with Laboratory Tests**

Elevated serum amylase levels may be observed temporarily following administration of the product and can interfere with the diagnosis of pancreatitis.

At high dosages the dilutional effects may result in decreased levels of coagulation factors and other plasma proteins and a decrease in hematocrit.

## 6 ADVERSE REACTIONS

### 6.1 Overall Adverse Reaction Profile

From the accumulated clinical development experience, expected adverse reactions after administration of Voluven® occurring in less than 10% of patients are as follows:

*Immune system disorders (Rare, >0.01% to <0.1%):* Products containing hydroxyethyl starch may lead to anaphylactoid reactions (hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema). In the event of an intolerance reaction, the infusion should be discontinued immediately and the appropriate emergency medical treatment initiated. [see *General Warnings and Precautions* (5.1)]

*Skin and subcutaneous tissue disorders (Common, >1 to <10%, dose dependent):* Prolonged administration of high dosages of hydroxyethyl starch may cause pruritus (itching) which is an undesirable effect observed with all hydroxyethyl starches.

*Investigations (Common, >1% to <10%, dose dependent):* The concentration of serum amylase can rise during administration of hydroxyethyl starch and can confound the diagnosis of pancreatitis. At high doses the dilutional effects may result in decreased levels of coagulation factors and other plasma proteins and in a decrease of hematocrit. [see *Interference with Laboratory Tests* (5.3)]

### 6.2 Adverse Reactions in Clinical Trials

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug may not reflect the rates observed in practice.

During clinical development, 471 patients were exposed to Voluven®, and a total of 768 patients received the hydroxyethyl starch 130/0.4 drug substance contained in Voluven® at different concentrations (2%, 4%, 6%, or 10%) and at cumulative doses of several mL up to 66 L<sup>1)</sup>. The mean duration of treatment with hydroxyethyl starch 130/0.4 was  $3.9 \pm 3.3$  days, mean cumulative doses were  $3338 \pm 3695$  mL, and the longest follow-up period was 90 days.

In the US trial, 100 patients undergoing elective orthopedic surgery were treated either with Voluven® (N=49) or hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) (N=51) for intraoperative volume replacement. Mean infusion volumes were  $1613 \pm 778$  mL for Voluven® and  $1584 \pm 958$  mL for hetastarch.

*Adverse reactions observed in at least 1% of patients:* In the US trial comparing Voluven® with hetastarch, a possible relationship to Voluven® was reported in five cases in a total of three patients (aPTT elevated, PT prolonged, wound hemorrhage, anemia, pruritus). A possible relationship to hetastarch was reported in five patients (three cases of coagulopathy; two cases of pruritus). The three coagulopathy cases in the hetastarch group were serious and occurred in patients receiving more than the labeled ceiling dose (20 mL/kg), whereas no serious coagulopathy occurred in the Voluven® group.

### 6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Voluven® and other types of hydroxyethyl starch solutions. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The safety profile from postmarketing experience of Voluven® is not different from the profile obtained from clinical trials performed using the product.

Based on spontaneous reporting of hypersensitivity reactions, urticaria, bronchospasm, or hypotension were the most frequently reported serious adverse drug reactions for patients treated with Voluven®.

With the administration of hydroxyethyl starch solutions, disturbances of blood coagulation can occur depending on the dosage<sup>2)</sup>.

## 7 DRUG INTERACTIONS

No interactions with other drugs or nutritional products are known.

The safety and compatibility of other additives have not been established [see *Directions for Use of Voluven®* (2.3)].

## 8 USE IN SPECIAL POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. Voluven® has been shown to cause embryocidal or other adverse effects in rats and rabbits when given in doses 1.7 times the human dose. There are no adequate and well-controlled studies in pregnant women. Voluven® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The type of hydroxyethyl starch present in Voluven® had no teratogenic properties in rats or rabbits. At 5 g/kg of body weight per day, administered as a bolus injection, fetal retardations and embryo-lethal effects were observed in rats and rabbits, respectively. In rats, a bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. All adverse effects were seen exclusively at maternal toxic doses due to fluid overload. [see *Toxicology* (13.2.1)]

Fertility studies on directly exposed animals have not been conducted.

### 8.2 Labor and Delivery

Information on the use of Voluven® during labor or delivery is unknown.

### 8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Voluven® is administered to a nursing woman.

### 8.4 Pediatric Use

In one trial, children including newborns to infants (< 2 years) undergoing elective surgery were randomized to receive Voluven® (N=41) or 5% albumin (N=41). The mean dose of Voluven® administered was  $16 \pm 9$  mL/kg<sup>3)</sup>.

Voluven® may be given to premature infants and newborns only after a careful risk/benefit evaluation. The safety and efficacy of Voluven® have not been established in the age group of 2 to 12 years. Use of Voluven® in children > 12 years is supported by evidence from adequate and well-controlled studies of Voluven® in adults and by data from children < 2 years old. Dosage in children should be adapted to individual patient colloid needs, taking into account underlying disease, hemodynamics and hydration status. [see *Pediatric Dose* (2.2)]

#### **8.5 Geriatric Use**

Of the total number of subjects in clinical studies of Voluven® (N= 471), 32% were 65 years old and older while 7% were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

#### **8.6 Renal impairment**

Voluven® is mainly excreted by the kidneys, and the risk of adverse reactions may be greater in patients with impaired renal function. Volume status, infusion rate, and urine output should be closely monitored. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. [see *Pharmacokinetics* (12.3)]

### **9 DRUG ABUSE AND DEPENDENCE**

Voluven® is not considered to be a drug of abuse potential.

### **10 OVERDOSAGE**

As with all plasma volume substitutes, overdosage can lead to overloading of the circulatory system (e.g. pulmonary edema). In this case, the infusion should be stopped immediately and if necessary, a diuretic should be administered. [see *General Warnings and Precautions* (5.1)]

### **11 DESCRIPTION**

Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) is a clear to slightly opalescent, colorless to slightly yellow, sterile, non-pyrogenic, isotonic solution for intravenous administration using sterile equipment.

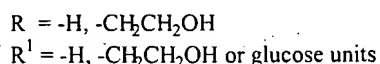
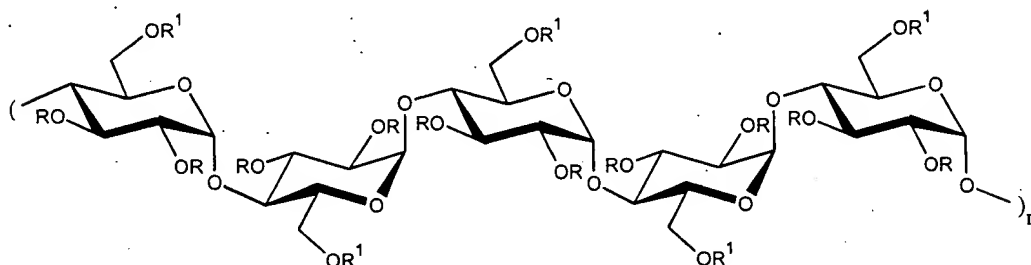
Each 100 mL of the solution contains:

|                             |        |
|-----------------------------|--------|
| Hydroxyethyl Starch 130/0.4 | 6 g    |
| Sodium Chloride USP         | 900 mg |
| in Water for Injection USP  |        |

pH adjusted with Sodium Hydroxide USP  
or Hydrochloric Acid USP

Electrolytes (mEq/L): Sodium 154, Chloride 154. pH 4 to 5.5. Calculated osmolarity 308 mOsmol/L.

The hydroxyethyl starch contained in Voluven<sup>®</sup> is a synthetic colloid for use in plasma volume replacement. The chemical name of hydroxyethyl starch is poly(O-2-hydroxyethyl) starch. The structural formula of hydroxyethyl starch is



Voluven<sup>®</sup> is packaged in 500 mL flexible plastic containers (**freeflex<sup>®</sup>**). **Freeflex<sup>®</sup>** is a flexible container made from coextruded polyolefin and is free of PVC, plasticizers, adhesives or latex (Non-DEHP, Latex-free). The **freeflex<sup>®</sup>** container offers an air-closed system and can be used with non-vented IV sets which prevent external air contamination. **Freeflex<sup>®</sup>** is collapsible and can be used in emergency cases for pressure infusion.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Voluven<sup>®</sup> contains hydroxyethyl starch in a colloidal solution which expands plasma volume when administered intravenously. This effect depends on the mean molecular weight (130,000 daltons; range 110,000 – 150,000 daltons), the molar substitution by hydroxyethyl groups (0.4; range 0.38 – 0.45) on glucose units of the starch, the pattern of hydroxyethyl substitution (C<sub>2</sub>/C<sub>6</sub> ratio) of approximately 9:1, and the concentration (6%), as well as the dosage and infusion rate.

Hydroxyethyl starch is a derivative of thin boiling waxy corn starch, which mainly consists of a glucose polymer (amylopectin) predominately composed of α-1-4-connected glucose units with several α-1-6-branches. Substitution of hydroxyethyl groups on the glucose units of the polymer reduces the normal degradation of amylopectin by α-amylase in the body. The low molar substitution (0.4) is the main pharmacological determinant for the beneficial effects of Voluven<sup>®</sup> on pharmacokinetics, intravascular volume and hemodilution<sup>4)</sup>. To describe the molecular weight and molar substitution characteristics of the hydroxyethyl starch in Voluven<sup>®</sup>, the compound is designated as hydroxyethyl starch 130/0.4.

## 12.2 Pharmacodynamics

After isovolemic exchange of blood with 500 mL of Voluven® in healthy volunteers, blood volume is maintained for at least 6 hours.

## 12.3 Pharmacokinetics

The pharmacokinetic profile of hydroxyethyl starch is complex and largely dependent on its molar substitution as well as its molecular weight<sup>4)</sup>. When administered intravenously, molecules smaller than the renal threshold (60,000-70,000 daltons) are readily and rapidly excreted in the urine, while molecules with higher molecular weights are metabolized by plasma  $\alpha$ -amylase prior to excretion via the renal route.

The mean *in vivo* molecular weight of Voluven® in plasma is 70,000 – 80,000 daltons immediately following infusion and remains above the renal threshold throughout the treatment period.

Following intravenous administration of 500 mL Voluven® to healthy volunteers, plasma levels of Voluven® remain at 75% of peak concentration at 30 minutes post-infusion and decrease to 14% at 6 hours post-infusion. Plasma levels of Voluven® return to baseline levels 24 hours following infusion. Plasma clearance, volume of distribution, and elimination half-life of Voluven® in healthy volunteers following IV administration of 500 mL were 31.4 mL/min, 5.9 liters, and 12 hours, respectively. Approximately 62 % of Voluven® was excreted as hydroxyethyl starch molecules in urine within 72 hours.

The pharmacokinetics of Voluven® are similar following single and multiple dose administration. No significant plasma accumulation occurred after daily administration of 500 mL of a 10% solution containing hydroxyethyl starch 130/0.4 over a period of 10 days. Approximately 70% of Voluven was excreted as hydroxyethyl starch molecules in urine within 72 hours.

### Renal Impairment:

Following a single intravenous administration of Voluven® (500 mL) in subjects with varying degrees of renal dysfunction, the AUC and clearance of Voluven® increased by 73% and decreased by 42% in patients, respectively, with creatinine clearance <50 mL/min as compared to patients with creatinine clearance >50 mL/min. However, terminal half-life and peak hydroxyethyl starch concentration were not affected by renal impairment. Plasma levels of Voluven® returned to baseline levels 24 hours following infusion. Approximately 59 % and 51 % of Voluven® were excreted as hydroxyethyl starch molecules in urine within 72 hours in patients with creatinine clearance  $\geq$ 30 mL/min and <30 mL/min, respectively.

There are no data available on the use of Voluven® in patients undergoing hemodialysis.

Pharmacokinetic data in patients with hepatic insufficiency or in pediatric or geriatric patients are not available. Effects of gender or race on the pharmacokinetics of Voluven® have not been studied.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals to evaluate the carcinogenic potential of Voluven® have not been performed. No mutagenic effects were observed with hydroxyethyl starch 130/0.4 10% solution in the following tests on mutagenic activity: *Salmonella typhimurium* reverse mutation assay (*in vitro*), mammalian cells in the *in vitro* gene mutation assay, assessment of the clastogenic activity in cultured human peripheral lymphocytes (*in vitro*), bone marrow cytogenetic test in Sprague-Dawley rats.

Fertility studies on directly exposed animals have not been performed.

### **13.2 Animal Toxicology and Pharmacology**

#### **13.2.1 Toxicology**

Three-month repeat infusion toxicology studies were conducted in rats and dogs in which three groups of animals were administered daily intravenous infusion over three hours. Dosing volumes of either 60 or 90 mL/kg body weight of hydroxyethyl starch 130/0.4 (10% solution) or 90 mL/kg 0.9% sodium chloride injection were studied. Observed toxicity following repeat infusion of hydroxyethyl starch is consistent with the oncotic properties of the solution resulting in hypervolemia in the animals. There were no apparent gender-related effects on toxicity following repeat administration of hydroxyethyl starch 130/0.4 in rats or dogs.

In reproduction studies in rats and rabbits, hydroxyethyl starch 130/0.4 (10% solution) had no teratogenic properties. Embryo-lethal effects were observed in rabbits at 5 g/kg body weight/day. In rats, bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. Signs of fluid overload were seen in the dams. Hydroxyethyl starch 130/0.4 (10% solution) was observed to have no effect in studies assessing skin sensitization, antigenicity, and blood compatibility.

#### **13.2.2 Pharmacology**

The pharmacodynamic effect of Voluven® was examined in a hemorrhagic shock model in conscious rats and a hemodilution model in dogs. In both studies the control group received pentastarch (6% hydroxyethyl starch 200/0.5).

Voluven® was as effective as pentastarch in maintaining cardiopulmonary function during isovolemic hemodilution in beagle dogs. In the three-hour follow-up period no additional administration of colloid was necessary.

There were no differences in long-term survival of rats after a single administration of Voluven<sup>®</sup> and pentastarch solutions following induced hemorrhagic shock (67% and 50% blood loss). In the 67% induced bleeding group receiving Voluven<sup>®</sup> (N=6), the survival rate was 83% which is within the normal range for this type of experiment. In the corresponding pentastarch group, survival was 100%. Infusion of Ringer's lactate resulted in a 50% survival rate after a 50% blood loss and a 0% survival after a 67% blood loss.

After multiple intravenous infusions of 0.7 g per kg body weight per day of 10% hydroxyethyl starch 130/0.4 or 10% hydroxyethyl starch 200/0.5 solution during 18 consecutive days, the plasma hydroxyethyl starch concentration in rats treated with hydroxyethyl starch 130/0.4 was lower compared to rats treated with hydroxyethyl starch 200/0.5. Hydroxyethyl starch 130/0.4 was eliminated faster than hydroxyethyl starch 200/0.5. In both groups, clear signs of hydroxyethyl starch tissue storage were detected in lymph nodes and spleen. Numerous empty vacuoles in macrophages were observed. Only minimal cellular vacuolization was found in the liver and kidney. Histochemical differences between the groups were not observed.

A study with 10% radiolabeled <sup>14</sup>C-hydroxyethyl starch 130/0.4 and 10% <sup>14</sup>C-hydroxyethyl starch 200/0.5 solutions was carried out<sup>6)</sup>. In animals treated with hydroxyethyl starch 130/0.4, radioactivity decreased from 4.3% of the total administered dose (2.6 g hydroxyethyl starch 130/0.4 per animal) on day 3 to 0.65% on day 52. In animals treated with hydroxyethyl starch 200/0.5, the <sup>14</sup>C-activity decreased from 7.7% of the total administered dose (2.7 g hydroxyethyl starch 200/0.5 per animal) on day 3 to 2.45% on day 52. These results confirm the faster elimination and lower persistence of hydroxyethyl starch 130/0.4 in tissue.

## 14 CLINICAL STUDIES

Voluven<sup>®</sup> was studied in controlled clinical trials in adult and pediatric surgical patients and in patients in intensive care units. Clinical studies included patients undergoing various types of surgery (orthopedic, urologic, cardiac) and trauma intensive care for situations in which hypovolemia is treated (pre-, intra-, and postoperative) or prevented (autologous blood donation, acute normovolemic hemodilution, hypervolemic hemodilution before cardiac surgery). The safety and efficacy of Voluven<sup>®</sup> were compared to other colloidal plasma substitutes [pentastarch (6% hydroxyethyl starch 200/0.5), hetastarch (6% hydroxyethyl starch 450/0.7), gelatin solution or human serum albumin] in studies carried out in common clinical settings of volume replacement therapy. Perioperative fluid administration of Voluven<sup>®</sup> ranged from 500 to 4500 mL/day in surgical patients, and cumulatively, 6 to 66 L during stays in intensive care units following traumatic brain injury.

A prospective, controlled, randomized, double-blind, multi-center trial of 100 patients undergoing elective orthopedic surgery was conducted in the US evaluating Voluven<sup>®</sup> (N=49) compared to hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) (N=51) for intraoperative volume replacement therapy<sup>7)</sup>. The primary efficacy variable, total volume of colloid solution required for intraoperative volume replacement therapy, was equivalent for the two treatment groups. Mean volume infused was 1613 ± 778 mL for Voluven<sup>®</sup> and 1584 ± 958.4 mL for hetastarch. The ratio Voluven<sup>®</sup>/hetastarch was estimated as 1.024 with a 95%

confidence interval (0.84, 1.25), which was included within the equivalence range of (0.55, 1.82) prespecified in the study protocol. This indicated that Voluven® and hetastarch have similar efficacy as intraoperative volume replacement therapy in major orthopedic surgery.

A second objective of the trial was to show superiority for safety between Voluven® and hetastarch. Four safety endpoints were prospectively defined and compared in a sequential manner (in order to preserve the type-I error rate, i.e., observing a difference where none actually exists). Per protocol, if there was no difference found between treatment arms for the first safety endpoint (EBL), the remaining endpoints were to be considered exploratory analyses requiring additional studies for confirmation.

Overall, no significant differences in serious adverse events were noted between the two treatment arms, but three cases of serious coagulopathy occurred in the hetastarch treatment arm. All three subjects received high doses (>3000 mL; labeled ceiling dose = 20 mL/Kg) of the product, which are known to increase the risk of bleeding. Since EBL for the two treatment arms was not statistically different (95% confidence interval includes unity), the difference observed for Factor VIII (see table, below) must be interpreted with caution. An exploratory analysis of total erythrocyte volume transfused (8.0 mL/kg vs. 13.8 mL/kg, Voluven® vs hetastarch, respectively) must also be viewed with caution.

**Table: Safety Variables for Study HS-13-30-US**

| Variable                           | Mean            |                    | Ratio VOLUVEN/Hetastarch |                |
|------------------------------------|-----------------|--------------------|--------------------------|----------------|
|                                    | VOLUVEN<br>N=49 | Hetastarch<br>N=51 | Estimate                 | 95% CI         |
| Calculated red blood cell loss [L] | 1.17            | 1.31               | 0.910                    | [0.720; 1.141] |
| Factor VIII [%]*                   | 100.5           | 81.4               | 1.244                    | [1.000; 1.563] |
| von Willebrand factor [%]*         | 97.7            | 88.7               | 1.128                    | [0.991; 1.285] |
| Fresh frozen plasma [mL]*          | 72              | 144                | 0.723                    | [0.000; 2.437] |

\*Exploratory analyses

There was no statistically significant difference between the two treatment groups with respect to the secondary efficacy endpoints of hemodynamic stability, body temperature,

hemodynamic parameters, blood pressure, central venous pressure, heart rate, fibrinogen and platelet count.

In addition to the US trial, three non-US trials were conducted with the primary objective of showing equivalency (based on mean difference rather than mean ratio as in the US study) between Voluven® and pentastarch in maintaining or restoring hemodynamic parameters. The largest of the three trials (N=100) met the prespecified boundary (-500 mL, 500 mL), but the two smaller studies (N=52 and N=59) did not.

In exploratory analyses, the effect of Voluven® on coagulation parameters (von Willebrand factor, Factor VIII, and Ristocetin cofactor) was shown to be significantly lower than pentastarch at one or more time points (US and non-US trials). These findings are consistent with the lower molar substitution, lower average molecular weight and narrower molecular weight distribution of Voluven® as compared to pentastarch resulting in a lower *in vivo* molecular weight and increased elimination from the circulation.

A safety profile of Voluven® at least as favorable as for pentastarch was also demonstrated in studies where Voluven® was administered at doses higher (up to 50 mL/kg or 3 g/kg) than for pentastarch (up to 33 mL/kg or 2 g/kg) in clinical settings where large or repetitive doses are administered. [see *Adverse Reactions* (6)]

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- 2) Kozek-Langenecker S. Effects of hydroxyethyl starch solutions on hemostasis. *Anesthesiology* 2005; 103 (3): 654-60
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- 4) Jungheinrich C, Neff T. Pharmacokinetics of hydroxyethyl starch. *Clin Pharmacokinetik* 2005; 44 (7): 681-699
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- 6) Leuschner J, Opitz J, Winkler A, Scharpf R, Bepperling F. Tissue storage of <sup>14</sup>C-labeled hydroxyethyl starch (HES) 130/0.4 and HES 200/0.5 after repeated intravenous administration to rats. *Drugs R D* 2003; 4 (6): 331-8

7) Gandhi SD, Weiskopf RB, Jungheinrich C et al. Volume replacement therapy during major orthopedic surgery using Voluven<sup>®</sup> (hydroxyethyl starch 130/0.4) or hetastarch. Anesthesiology 2007; 106:1120-1127

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

Voluven<sup>®</sup> (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) for intravenous infusion is supplied in the following primary container and carton sizes:

Polyolefin bag (*freeflex*<sup>®</sup>) with overwrap: 500 mL  
Carton of 15 x 500 mL  
NDC 0409-1029-01

Store at 15° to 25°C (59° to 77°F). Do not freeze.

#### 17 PATIENT COUNSELING INFORMATION

Because this product is not used directly by patients, patient counseling or instructions for use by patients is not considered necessary.

Manufactured by: Fresenius Kabi Norge AS,  
P.O. Box 430,  
NO-1753 HALDEN, NORWAY

Distributed by:  
Hospira, Inc.  
275 North Field Drive  
Lake Forest, Illinois 60045 USA

Made in Norway

EN-1597



## Product Approval Information - New Drug Applications

December 27, 2007

Our reference: NDA BN070012

Fresenius Kabi  
Attention: W. Gerald Cohn  
c/o Carolina Research Group, Inc.  
P.O. Box 32295  
Raleigh, NC 27622

Dear Mr. Cohn:

Please refer to your new drug application dated February 28, 2007 and received March 1, 2007, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for 6% Hydroxyethyl Starch in 0.9% Sodium Chloride Infusion (Voluven® 500 mL freeflex® flexible plastic intravenous solution container).

We acknowledge receipt of your submissions dated February 28; March 30; June 25 and 26; July 26; August 16 and 17; September 6 and 20; October 2, 4, 12, and 17; November 9, 14, 16, 27, and 30; and December 3 and 10, 2007

This new drug application provides for the use of 6% Hydroxyethyl Starch in 0.9% Sodium Chloride Infusion ((Voluven® 500 mL freeflex® flexible plastic intravenous solution container) for treatment and prophylaxis of hypovolemia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA BN070012.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

We remind you of your postmarketing study commitments in your submission dated November 30, 2007. The commitments are listed below.

1. To perform a multiple-dose randomized controlled trial (RCT) to be conducted in

subjects with severe sepsis including subjects with renal dysfunction and at risk for deterioration of renal dysfunction. Fresenius Kabi will submit the final Clinical Study Protocol of this Phase 3b study entitled "Crystalloids or colloids in patients with severe sepsis: effects on hemodynamics and tolerability of enteral nutrition" (Short title: CRYSTMAS, study code 06-HE06-01) within 3 months of the Approval Letter and will submit the final Clinical Study Report to FDA within 36 months of the Approval Letter.

Protocol Submission: by within 3 months of the date of this letter

Final Report Submission: by within 36 months of the date of this letter

2. Fresenius Kabi commits to perform a randomized controlled trial (RCT) to be conducted in children in the age group of 2 to 12 years. Fresenius Kabi will submit the final Clinical Study Protocol of this Phase 3 study entitled "Efficacy and safety of 6 % hydroxyethyl starch 130/0.4 ((Voluven®) vs 5% HSA in volume substitution therapy during open-heart surgery in 2 to 12 years old pediatric patients" within 12 months of the Approval Letter and will submit the final Clinical Study Report to FDA within 36 months of the Approval Letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Blood Applications and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Advertising and Promotional Labeling Branch (HFM-602)  
1401 Rockville Pike, Suite 200 North  
Rockville, MD 20852-1448

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm).

FDA has determined that referral of this application to the Blood Products Advisory Committee (BPAC) prior to approval (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]) was not needed for the following reasons: Voluven®'s mechanism of action as a plasma volume expander indicated for the treatment and prophylaxis of hypovolemia is well studied and understood. The European-approved Voluven® product manufactured by Fresenius Kabi has demonstrated comparable safety and efficacy with similar products, such as hetastarch and pentastarch. Studies to evaluate the efficacy of Voluven® were adequate and the results did not raise any concerns related to safety. Review of information submitted in the NDA for Voluven® did not raise any controversial issues or pose unanswered scientific questions which would have benefited from advisory committee discussion and recommendations.

If you have any questions, please contact Franklin T. Stephenson, Regulatory Project Manager, at (301) 827-6165.

Sincerely,

/signed/

Jay S Epstein, M.D.  
Director Office of Blood Research and Review  
Center for Biologics  
Evaluation and Research

Enclosure: Package Insert (PDF, 233 KB)

Updated: December 27, 2007



US005218108A

**United States Patent** [19]

Sommermeyer et al.

[11] Patent Number: 5,218,108

[45] Date of Patent: Jun. 8, 1993

[54] **HYDROXYLETHYLSTARCH (HES) AS  
PLASMA EXPANDER AND PROCESS FOR  
PREPARING HES**

[75] Inventors: Klaus Sommermeyer; Franz Cech;  
Burghard Weidler, all of Rosbach;  
Klaus Henning, Usingen, all of Fed.  
Rep. of Germany

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[21] Appl. No.: 533,294

[22] Filed: Jun. 5, 1990

[30] Foreign Application Priority Data.

Jun. 16, 1989 [DE] Fed. Rep. of Germany ..... 3919729

[51] Int. Cl.<sup>5</sup> ..... C08B 31/10; A61K 31/72

[52] U.S. Cl. .... 536/111; 514/60

[58] Field of Search ..... 536/111; 514/60

[56] References Cited

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4,716,186 12/1987 Portnoy et al. .... 536/111  
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**FOREIGN PATENT DOCUMENTS**

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Primary Examiner—Nathan M. Nutter  
Attorney, Agent, or Firm—Omri M. Behr; Matthew J.  
McDonald

[57] **ABSTRACT**

A hydroxyethyl starch for use as plasma expander which is obtainable by hydrolytic predegradation of a starch rich in amylopectin, partial hydroxyethylation to a specific substitution degree in the presence of alkali and subsequent hydrolytic degradation to a specific molecular weight, comprises a mean molecular weight of 60,000–600,000 and a substitution degree MS of 0.15–0.5. The ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8–20 and the substitution degree DS lies in the range from 0.15 to 0.5. A process for the preparation of this hydroxyethyl starch employs 2-chloroethanol as hydroxyethylation agent. The hydroxyethylation is carried out under alkaline conditions at room temperature, the pH value held at a value of about 12 and the temperature held at a value of about 20° C.

7 Claims, No Drawings

# HYDROXYLETHYLSTARCH (HES) AS PLASMA EXPANDER AND PROCESS FOR PREPARING HES

The field of volume substitution (e.g. hemorrhagic shock) or hemodilution (e.g. arterial occlusive disease, Fontaine II B, III) is today inconceivable without the use of colloidal plasma substitutes. For both these indications, of the exogeneous plasma substitutes (starch, gelatins, dextran), hydroxyethyl starch (HES) has found the greatest acceptance in recent years.

The lower disturbance of coagulation and the clearly reduced incidence of serious anaphylactoid reactions compared with dextran are responsible for the good acceptance of hydroxyethyl starch in the field of volume replacement and hemodilution. In addition, it has been possible to show that the volume efficacy of hydroxyethyl starch, depending on the indication, may be referred to as sufficient to good, a differentiated therapy being possible, depending on the state of the patient, by using the various known hydroxyethyl starch preparations differing in molecular weight and substitution degree. The factor considered particularly favourable here is the low colloid osmotic pressure of starch solutions compared with dextrans. With regard to the kidneys, the lower urine viscosity involves a lesser risk of a decrease in functional activity. In the area of hemodilution, in addition to the reduction of hematocrit, the reduction of plasma viscosity in particular has proved to be a therapeutically effective principle of HES-induced rheological improvement. Therapeutical advantages are obtained over other exogeneous plasma substitutes.

Already known hydroxyethyl starches used as plasma expanders have different molecular weights  $M_w$  and substitution degrees MS and DS as well as different substitution patterns.

Due to the use of the natural starting raw material amylopectin and the production process in which to a certain extent a cleaving of the polymer chains is necessary, the hydroxyethyl starch is not present as molecular unitary substance with defined molecular weight but as mixture of molecules of different size which are also differently substituted by hydroxyethyl groups. The characterization of such mixtures requires the aid of statistically determined magnitudes (cf. K. Sommermeyer et al., "Clinically employed hydroxyethyl starch: physical chemical characterization", Krankenhauspharmazie, 271 (1987)). To denote the average molecular weight, the mean molecular weight  $M_n$  is used. The general definition of this mean value is:

$$M_n = \frac{\sum N_i \cdot M_i}{\sum N_i}$$

There are two differently defined substitution degrees for defining the substitution by hydroxyethyl groups.

The substitution degree MS (molar substitution) is defined as the average number of hydroxyethyl groups per anhydroglucose unit. It is determined from the total number of hydroxyethyl groups in a specimen, for example in accordance with Morgan, by ether splitting and subsequent quantitative determination of ethyl iodide and ethylene, which are thereby formed.

In contrast, the substitution degree DS (degree of substitution) is defined as the proportion of the substi-

tuted anhydroglucose units of all anhydroglucose units. It can be determined from the measured amount of the unsubstituted glucose after hydrolysis of a specimen. It follows from these definitions that  $MS > DS$ . In the case where only monosubstitution is present, i.e. each substituted anhydroglucose unit carries only one hydroxyethyl group,  $MS = DS$ .

It is known that  $\alpha$ -amylase breaks down hydroxyethyl starches in the sense that only glycosidic bonds of unsubstituted anhydroglucose units are split. It is further known that with increasing degree of substitution MS or DS the elimination of hydroxyethyl starches from the plasma is retarded.

It is moreover known that for the same MS, DS and the same molecular weight distribution starches substituted mainly in the 6-position are eliminated faster than starches substituted mainly in the 2-position.

In this respect, only hydroxyethyl starches having a low C2/C6 ratio or being highly substituted were used for pharmaceutical purposes.

Thus, GB-PS 1,395,777 describes hydroxyethyl starches substituted predominantly in 6-position corresponding to a C2/C6 ratio of 0.5 to 2.0. These hydroxyethyl starches are made by reaction of wax maize starch with ethylene oxide with alkali in excess.

DE-OS 2,814,032 describes a process for preparing hydroxyl starch suitable as blood plasma expander, the starch being alkaline hydroxyethylated; the reaction mixture then neutralized and the hydroxyethyl starch formed extracted from the reaction mixture with a solvent, such as dimethyl formamide in which the salts formed by the neutralization are only sparingly soluble or not soluble at all. The hydroxyethyl starch obtained has a molar ratio of 2-O-hydroxyethyl anhydroglucose to 6-O-hydroxyethyl anhydroglucose of about 1.

According to the process described in DE-OS 3,313,600 for preparing plasma expanders on a starch basis in which the degradation step of the starch rich in amylopectin is at least partially carried out enzymatically, the breaking down of the starch is performed to a molecular weight of 40,000 to 1,000,000 Dalton, in particular from 200,000 to 450,000 Dalton, and the etherification to a substitution degree (MS) of 0.1 to 0.8 or 0.5 to 0.8, in particular 0.5 to 0.7 (cf. page 8, paragraph 3). The ratio of the substitution of C2 compared with the substitution of C6 is low (cf. page 5, paragraph 2).

The aforementioned hydroxyethyl starches have the disadvantage that they do not ensure a complete degradability from the plasma within a period of about 6-12 hours and moreover, due to their high substitution degree MS ( $MS > 0.5$ ), involve the danger that with the usual repetition infusions over longer periods of time an accumulation of difficultly eliminatable components takes place in the serum and tissue. Due to this long-time storing, allergic reactions may occur, for example nettle rash, etc.

The problem underlying the invention is therefore to make available a hydroxyethyl starch which can be completely broken down within a physiologically reasonable time.

A further problem resides in making available an HES which nevertheless due to the choice of a suitable MS or DS value and the molecular weight has a controllable elimination behaviour.

The starting products for recovering hydroxyethyl starch are starches having a high content of amylopectin, the highly branched component of starch, in partic-

ular potato starch, wax maize starch, sorghum starch or waxy rice starch.

For a coarse presetting of the intended molecular weight these starches are subjected to a hydrolytic degradation reaction. The molecular weight is reduced here from about 20,000,000 Dalton to several million Dalton.

In the subsequent alkaline hydroxyethylation with known hydroxyethylation agents, it is possible to introduce a hydroxyethyl group into position 2, 3 and 6 of the anhydroglucose unit. Disubstituted units, such as 2,3-dihydroxyethyl anhydroglucose, 2,6-dihydroxyethyl anhydroglucose are formed in the synthesis with less probability. The reactivity of the individual hydroxy groups in the unsubstituted anhydroglucose unit compared with hydroxyethylation is different depending on the reaction conditions. Within certain limits, the substitution pattern, i.e. the individual differently substituted anhydroglucoses statistically shared amongst the individual polymer molecules, can thereby be influenced. Advantageously, predominantly the 2 and the 6-position is hydroxyethylated, the 6-position being preferred due to easier accessibility.

The objective of the present invention, that is the preparation of a hydroxyethyl starch which can be completely broken down within a physiologically reasonable period and which on the other hand nevertheless has a controllable elimination behaviour, is achieved by a starch substituted predominantly in 2-position and substituted as homogeneously as possible, MS being approximately equal to DS.

The predominant 2-substitution makes the hydroxyethyl starch relatively difficult to degrade for  $\alpha$ -amylase. It is advantageous to avoid as far as possible the occurrence of substituted anhydroglucose units one behind the other within the polymer molecule in order to guarantee complete degradability.

This can be achieved in that the substitution is accordingly low, enabling the molecules to derivate statistically in the sense of a substitution distributed over the total molecules. This results in substituted anhydroglucoses at a relatively large distance apart, compensating the effect of the retardation of the  $\alpha$ -amylase degradation due to the predominant 2-substitution and enabling a controllability of the degradation rate to be achieved.

It has been found that hydroxyethyl starches substituted extremely low ( $MS < 0.5$ ) and having a high ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units are rapidly and completely eliminated from the human body within the first hours of the infusion.

It has further been found that such hydroxyethyl starches, in spite of the low substitution, contrary to the opinion of those skilled in the art, do have an adequately high solubility in aqueous medium so that the solutions are stable even for relatively long periods of time and do not form any agglomerates or gels which would make the further use as plasma expander solution impossible.

Hydroxyethyl starches with the characteristics described above therefore combine the general advantages of hydroxyethyl starch compared with other plasma expander types, such as gelatins or dextran, and avoids the disadvantages of the hitherto known hydroxyethyl starch types used for the indications described.

Hydroxyethyl starches having the aforementioned properties can be obtained with the aid of a process including essentially the following steps:

a) Preextraction of the starch used with methanol to remove vegetable dyes and to block reactive groups. Thus, for example, reactive aldehyde groups are partially inactivated by acetal formation.

b) Methanolic hydrolysis for coarse setting of the molecular weight with a 20-40%, preferably 30% methanolic suspension of the starch with 1% HCl, the latter being held for 2-4 h, preferably 3 h, at 30°-50° C., preferably 40° C. The end of the reaction is achieved by neutralization with 1 NaOH and subsequent cooling to room temperature. Thereafter the suspension is washed free of chloride.

c) Alkali wash for protein extraction, a 30-50%, preferably 40% suspension in 0.1 N NaOH being prepared and this being held 1-3 h, preferably 2 h, at 30°-50° C., preferably 40° C. Thereafter the procedure is repeated at room temperature.

d) Hydroxyethylation with a hydroxyethylating agent, for example ethylene oxide, and in a particularly preferred embodiment, 2-chloroethanol, the molar ratio of pretreated starch to hydroxyethylating agent being adapted to the desired substitution degree. The starch is dissolved under nitrogen in 20-40%, preferably 30% suspension, in 1 N NaOH for 2 h at 30°-50° C., preferably 40° C. Within 6-10 hrs., preferably 7-8 hrs., the hydroxyethylating agent is added in drops at room temperature, the addition of 10 N NaOH preventing the pH value dropping below 12. Thereafter, this is neutralized with 10% HCl.

e) The solution is heated to 40°-70° C., preferably 60° C., mixed with 0.2% HCl and the hydrolysis followed viscosimetrically. The reaction is terminated by neutralization with NaOH and cooling to room temperature.

f) Purification by filtration through a depth filter and ultrafiltration through a hollow fibre module with a separating limit of about 30,000 Dalton.

g) Spray drying of the end products in a manner known per se.

The hydroxyethyl starches according to the invention are also suitable as carbohydrate components in enteral nutrition of diabetics because the same considerations apply as regards the degradability.

The invention will be explained in detail hereinafter with the aid of an example.

500 g wax maize starch is suspended in a litre of dry methanol and brought to boil. After cooling the methanol is sucked off and the starch washed with water. The washing operation is repeated once.

The starch with a residual moisture content of 28.13% is hydrolyzed in 30% methanolic suspension with 1% HCl for three hours at 40° C. The reaction is stopped by neutralization with 1 N NaOH in methanol and cooling to room temperature. After extraction the starch exhibits a residual moisture content of 16.12% and a mean molecular weight of 900,000.

The starch is suspended in a litre H<sub>2</sub>O, extracted and washed free of chloride. After suction drying the starch has a residual moisture content of 51.29%.

The starch is thereafter stirred in 40% suspension in 0.1 N NaOH for 2 hours at 40° C., again cooled to room temperature and dried by exhaustion (residual moisture content 48.60%). The operation is repeated once at room temperature.

418.0 g (2.58 Mol) of pretreated starch are dissolved in 30% suspension in 1 N NaOH at 40° C. under nitro-

gen. Within 7-8 hrs., 51.9 ml (0.77 Mol) 2-chloroethanol is dripped in. By adding NaOH reduction of the pH value below 12 is avoided. Thereafter, neutralization is carried out with 10% HCl.

The solution is filtered after 1:1 dilution with water via a depth filter (Seitz T750).

The solution is thereafter heated to 60° C., set with 25% HCl to an HCl concentration of 0.2 and hydrolyzed for 4 hours.

The solution is neutralized by addition of sodium hydroxide to pH 6.0 and cooled to room temperature. Thereafter, filtration is carried out via a Seitz EKS filter.

The clear solution is now ultrafiltrated via a hollow fibre module with a separation limit of about 30,000 Dalton and the remaining retentate spray dried.

A hydroxyethyl starch is obtained having a mean molecular weight of 234,000 and a molar substitution degree of 0.26. The C2/C6 ratio is 9.34. The hydroxyethyl starch prepared in this manner has the following substitution pattern (area percentages) which can be determined by complete hydrolysis of HES and subsequent determination of glucose and its hydroxyethyl derivatives via trimethyl silylation:

|                               |        |
|-------------------------------|--------|
| glucose:                      | 81.42% |
| 2-O-hydroxyethyl glucose:     | 12.42% |
| 3-O-hydroxyethyl glucose:     | 2.70%  |
| 6-O-hydroxyethyl glucose:     | 1.33%  |
| 2,2-O-dihydroxyethyl glucose: | 0.21%  |
| 2,3-O-dihydroxyethyl glucose: | 0.51%  |
| 2,6-O-dihydroxyethyl glucose: | 0.17%  |
| 3,3-O-dihydroxyethyl glucose: | 0.10%  |
| 3,6-O-dihydroxyethyl glucose: | 0.05%  |

We claim:

1. Hydroxyethyl starch for use as plasma expander obtainable by hydrolytic pre-degradation of a starch rich in amylopectin, partial hydroxyethylation up to a certain substitution degree in the presence of alkali and subsequent hydrolytic degradation to a certain molecular weight, characterized in that it has a mean molecular weight of 60,000-600,000 and a substitution degree MS of 0.15 to 0.5, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and

the substitution degree DS lies in the range from 0.15 to 0.5.

2. Hydroxyethyl starch according to claim 1, characterized in that it has a mean molecular weight of 80,000 to 400,000 and a substitution degree MS of 0.2-0.4, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.15 to 0.40.

3. Hydroxyethyl starch according to claim 1, characterized in that it has a mean molecular weight of 100,000 to 300,000 and a substitution degree MS of 0.25-0.35, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.2 to 0.35.

4. A hydroxyethyl starch for use as plasma expander characterized in that

it has a mean molecular weight of 60,000-600,000 and a substitution degree MS of 0.15 to 0.5,

the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.15 to 0.5, produced by a process wherein:

- a) starch having a content of amylopectin of >95% is pre-extracted with methanol,
  - b) the starch is brought by acid hydrolysis to a suitable mean molecular weight,
  - c) the starch is subjected to an alkali wash,
  - d) the starch is hydroxyethylated by means of a hydroxyethylation agent under alkaline conditions,
  - e) the molecular weight is exactly set by acid hydrolysis,
  - f) the hydroxyethyl starch thus obtained is pulled, and
  - g) spray dried,
- characterized in that the hydroxyethylation agent used is selected from the group consisting of 2-chloroethanol and ethylene oxide and the hydroxyethylation is carried out under alkaline conditions at room temperature.

5. A starch of claim 4 characterized in that the pH value is kept at a value of about 12 during the hydroxyethylation.

6. A starch of claim 4 characterized in that the temperature is kept at a value of about 20° to 25° C.

7. A starch of claim 4 characterized in that the hydroxyethyl starch is purified by filtration and ultrafiltration.

\* \* \* \* \*



# UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents  
United States Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450  
[www.uspto.gov](http://www.uspto.gov)

Customer No 359

ISTMT

DATE PRINTED  
02/05/2008

OMRI M. BEHR, ESQ.  
325 PIERSON AVENUE  
EDISON NJ 08837

## MAINTENANCE FEE STATEMENT

According to the records of the U.S. Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450.

| PATENT<br>NUMBER | FEE AMT    | SUR<br>CHARGE | PYMT<br>DATE | U.S.<br>APPLICATION<br>NUMBER | PATENT<br>ISSUE<br>DATE | APPL.<br>FILING<br>DATE | PAYMENT<br>YEAR | SMALL<br>ENTITY? | ATTY DKT<br>NUMBER |
|------------------|------------|---------------|--------------|-------------------------------|-------------------------|-------------------------|-----------------|------------------|--------------------|
| 5,218,108        | \$3,320.00 | \$0.00        | 11/24/04     | 07/533,294                    | 06/08/93                | 06/05/90                | 12              | NO               | LUDR3.0-036        |



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| PATENT<br>NUMBER | FEE AMT    | SUR<br>CHARGE | PYMT<br>DATE | U.S.<br>APPLICATION<br>NUMBER | PATENT<br>ISSUE<br>DATE | APPL.<br>FILING<br>DATE | PAYMENT<br>YEAR | SMALL<br>ENTITY? | ATTY DKT<br>NUMBER |
|------------------|------------|---------------|--------------|-------------------------------|-------------------------|-------------------------|-----------------|------------------|--------------------|
| 5,218,108        | \$1,950.00 | \$0.00        | 11/13/00     | 07/533,294                    | 06/08/93                | 06/05/90                | 08              | NO               | LUDR3.0-036        |



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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450.

| PATENT<br>NUMBER | FEE AMT    | SUR<br>CHARGE | PYMT<br>DATE | U.S.<br>APPLICATION<br>NUMBER | PATENT<br>ISSUE<br>DATE | APPL.<br>FILING<br>DATE | PAYMENT<br>YEAR | SMALL<br>ENTITY? | ATTY DKT<br>NUMBER |
|------------------|------------|---------------|--------------|-------------------------------|-------------------------|-------------------------|-----------------|------------------|--------------------|
| 5,218,108        | \$1,020.00 | \$0.00        | 11/25/96     | 07/533,294                    | 06/08/93                | 06/05/90                | 04              | NO               | LUDR3.0-036        |



**Fresenius  
Kabi**

### **Voluven 6 % Solution for Infusion**

Listing of the actual registrations within EU and Non-EU countries

| <b>Country</b>                    | <b>Reg-Date</b> | <b>Reg-No.</b> |
|-----------------------------------|-----------------|----------------|
| Germany<br>(Voluven)              | 22-Jun-1999     | 42093.00.00    |
| Germany<br>(Voluven<br>Fresenius) | 26-Aug-1999     | 45010.00.00    |
| Germany<br>(Voluven 6%)           | 26-Aug-1999     | 44943.00.00    |

Registrations based on the German marketing authorisation no. 42093.00.00

| <b>Country</b> | <b>Reg-Date</b> | <b>Reg-No.</b> |
|----------------|-----------------|----------------|
| Switzerland    | 27-Jun-2000     | 55093          |



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Food and Drug Administration  
1401 Rockville Pike  
Rockville MD 20852-1448

Our Reference: BB-IND 9740

April 5, 2001

Fresenius Kabi Deutschland, GmbH  
Attention: Rosemary P. Davis  
Manager Of Regulatory Affairs  
P.O. Box 597  
8484 US 70 West  
Clayton, NC 27520-0597



Dear Ms. Davis:

The Center for Biologics Evaluation and Research has received your **Investigational New Drug Application (IND)**. The following product name and BB-IND number have been assigned to this application. They serve only to identify it and do not imply that this Center either endorses or does not endorse your application.

BB-IND #: 9740

SPONSOR: **Fresenius Kabi Deutschland, GmbH**

PRODUCT NAME: **High Molecular Weight Hydroxyethyl Starch - 6% (Voluven)**

DATE OF SUBMISSION: **March 23, 2001**

DATE OF RECEIPT: **March 26, 2001**

This BB-IND number should be used to identify all future correspondence and submissions, as well as telephone inquiries concerning this IND. Please provide an **original and two copies of every submission to this file**. Please include three originals of all illustrations which do not reproduce well.

It is understood that studies in humans will not be initiated until 30 days after the date of receipt shown above. If this office notifies you, verbally or in writing, of serious deficiencies that require correction before human studies can begin, it is understood that you will continue to withhold such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory. If such a clinical hold is placed on this file, you will be notified in writing of the reasons for placing the IND on hold.

You are responsible for compliance with applicable portions of the Public Health Service Act, the Federal Food, Drug, and Cosmetic Act, and the Code of Federal Regulations (CFR). A copy of 21 CFR Part 312, pertaining to INDs, is enclosed. Copies of other pertinent regulations are

Page 2 - BB-IND 9740

available from this Center upon request. The following points regarding obligations of an IND sponsor are included for your information only, and are not intended to be comprehensive.

Progress reports are required at intervals not exceeding one year and are due within 60 days of the anniversary of the date that the IND went into effect. Any unexpected, fatal or immediately life-threatening reaction which is associated with use of this product must be reported to this Center within three working days, and all serious, unexpected adverse experiences must be reported, in writing, to this Center and to all study centers within ten working days.

Charging for an investigational product in a clinical trial under an IND is not permitted without the prior written approval of the FDA.

Prior to use of each new lot of the investigational biologic in clinical trials, please submit the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results).

If not included in your submission, please provide copies of the consent forms for each clinical study. A copy of the requirements for and elements of informed consent are enclosed. Also, please provide documentation of the institutional review board approval(s) for each clinical study.

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR Part 58, copies available upon request). If such studies have not been conducted in compliance with these regulations, please provide a statement describing in detail all differences between the practices used and those required in the regulations.

Item 7a of form FDA 1571 requests that either an "environmental assessment," or a "claim for categorical exclusion" from the requirements for environmental assessment, be included in the IND. If you did not include a response to this item with your application, please submit one. See the enclosed information sheet for additional information on how these requirements may be addressed.

Sponsors of INDs for products used to treat life-threatening or severely debilitating diseases are encouraged to consider the interim rule outlined in 21 CFR 312.80 through 312.88.

Telephone inquiries concerning this IND should be made directly to me at (301) 827-3524.

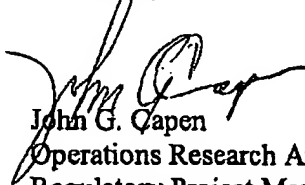
Correspondence regarding this file should be addressed as follows:

Center for Biologics Evaluation and Research  
ATTN: Office of Blood Research and Review  
HFM 99, Room 200N  
1401 Rockville Pike  
Rockville, MD 20852-1448

Page 3 - BB-IND 9740

If we have any comments after we have reviewed this submission, we will contact you.

Sincerely yours,



John G. Capen

Operations Research Analyst  
Regulatory Project Management Branch  
Division of Blood Applications  
Office of Blood Research and Review  
Center for Biologics Evaluation and Research

Enclosures (3):

21 CFR Part 312  
21 CFR 50.20, 50.25  
Information sheet on 21 CFR 25.24

***Regulatory Correspondence/Contacts Log***

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**2000**

**August 29, 2000**

**PRE-IND MEETING**

Clinical study design was discussed in detail and the FDA provided a number of specific recommendations on study design and size as well as on endpoints and other documentation to be captured in the study.

**2001**

**March 23, 2001**

**SUBMISSION OF IND (BB-IND 9740)**

**April 5, 2001**

**FDA ACKNOWLEDGES RECEIPT OF IND**

**May 30, 2001**

**RECEIPT OF FDA QUESTIONS AND REQUEST  
FOR PROTOCOL AMENDMENT**

**July 6, 2001**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 001)**

Response to FDA letter dated May 30, 2001

**September 2001**

**START OF PHASE III STUDY HS-13-30-US**

**August 2, 2001**

**SUBMISSION OF INFORMATION AMENDMENT  
(Serial No. 002)**

Submission of documentation for a compatibility study

***Regulatory Correspondence/Contacts Log***

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**2002**

**January 17, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 003)**

Submission of positive votes and final informed consent form for all centers

**May 8, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 004)**

**June 25, 2002**

Change in protocol  
**SUBMISSION OF ANNUAL REPORT  
(Serial No. 005)**

**July 17, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 006)**

Protocol signature of 2 new principal investigators

**September 16, 2002**

**FDA LETTER RECEIVED**

Questions and comments on IND submission dated May 8, 2002  
(Serial No. 004) obtained

**October 7, 2002**

**SUBMISSION OF RESPONSE TO FDA LETTER  
DATED SEPTEMBER 16, 2002  
(Serial No. 007)**

**December 16, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 008)**

Closing of a study center etc.

**2003**

**May 8, 2003**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 009)**

***Regulatory Correspondence/Contacts Log***

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Inclusion of additional subinvestigator etc.

**July 1, 2003**

**SUBMISSION OF INFORMATION AMENDMENT  
(Serial No. 010)**

Submission of documentation for a compatibility study

**July 22, 2003**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 011)**

**2004**

**June 24, 2004**

**REQUEST FOR PRE-NDA TYPE B MEETING  
(Serial No. 012)**

**July 5, 2005**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 013)**

**July 28, 2004**

**REQUEST FOR PRE-NDA TYPE B MEETING  
(Serial No. 014)**

**September 1, 2004**

**PRE-NDA MEETING WITH FDA**

Requested Pre-NDA Type B Meeting held with FDA

**October 19, 2004**

**SUBMISSION OF GENERAL CORRESPONDENCE  
(Serial No. 015)**

Designation of domestic agent

**October 20, 2004**

**SUBMISSION OF GENERAL CORRESPONDENCE  
(Serial No. 016)**

Study termination in all centers

***Regulatory Correspondence/Contacts Log***

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**2005**

**June 29, 2005**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 017)**

**2006**

**February 9, 2006**

**SUBMISSION OF GENERAL CORRESPONDENCE  
(Serial No. 018)**

Submission of safety data base

**July 13, 2006**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 019)**

**2007**

**September 14, 2007**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 020)**

***Regulatory Correspondence/Contacts Log***

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**2007****February 28, 2007****SUBMISSION****ORIGINAL NDA**

Submission of original NDA

**March 23, 2007****CORRESPONDENCE FROM FDA**

FDA acknowledges receipt of NDA on March 1, 2007

**March 30, 2007****TELECON FROM FDA**

FDA request additional copy of Module 3 and Methods Validation Package

**March 30, 2007****SUBMISSION****NDA COPIES**

Submission of requested copy of Module 3 and Methods Validation Package

**April 30, 2007****CORRESPONDENCE FROM FDA**

FDA advises that NDA is filed.

**June 11, 2007****TELECON FROM FDA**

FDA requested teleconference.

**June 11, 2007****FAX FROM FDA****INFORMATION  
REQUEST**

FDA sends fax to list questions of FDA reviewers.

**June 12, 2007****TELECONS TO/FROM FDA**

***Regulatory Correspondence/Contacts Log***

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|                      |  |                                 |
|----------------------|--|---------------------------------|
| <b>June 13, 2007</b> | <b>TELECON TO FDA</b>  |                                 |
| <b>June 13, 2007</b> | <b>EMAIL FROM FDA</b>  |                                 |
| <b>June 13, 2007</b> | <b>EMAIL TO FDA</b>  |                                 |
| <b>June 18, 2007</b> | <b>TELECONFERENCE WITH FDA</b>   |                                 |
| <b>June 18, 2007</b> | <b>EMAIL TO FDA</b>  |                                 |
| <b>June 18, 2007</b> | <b>EMAIL FROM FDA</b>  |                                 |
| <b>June 25, 2007</b> | <b>SUBMISSION</b>  | <b>NDA AMENDMENT</b>            |
|                      | Submission of response to FDA questions.                               |                                 |
| <b>June 26, 2007</b> | <b>SUBMISSION</b>  | <b>SAFETY UPDATE<br/>REPORT</b> |
|                      | Submission of first safety update report.<br>(Seven volume submission) |                                 |
| <b>June 28, 2007</b> | <b>EMAIL TO FDA</b>  |                                 |
| <b>June 29, 2007</b> | <b>EMAIL FROM FDA</b>  |                                 |
| <b>July 18, 2007</b> | <b>FAX FROM FDA</b>  | <b>INFORMATION<br/>REQUEST</b>  |

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**Regulatory Correspondence/Contacts Log**

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|                          |   |                                |
|--------------------------|---|--------------------------------|
| <b>July 26, 2007</b>     | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>           |
|                          | Submission of response to FDA questions presented in fax of July 18.                      |                                |
| <b>July 30, 2007</b>     | <b>FAX FROM FDA</b>   | <b>INFORMATION<br/>REQUEST</b> |
|                          | FDA sends fax to request information on CMC and clinical matters.                         |                                |
| <b>August 6, 2007</b>    | <b>TELECON TO FDA</b>   | <b>INFORMATION<br/>REQUEST</b> |
| <b>August 16, 2007</b>   | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>           |
|                          | Submission of response to FDA questions presented in fax of July 30.                      |                                |
| <b>August 17, 2007</b>   | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>           |
|                          | Submission of draft Summary Basis of Approval as requested by FDA in telecon of August 6. |                                |
| <b>August 21, 2007</b>   | <b>TELECON TO FDA</b>   | <b>ADMINISTRATIVE</b>          |
| <b>August 21, 2007</b>   | <b>EMAIL TO FDA</b>   | <b>ADMINISTRATIVE</b>          |
| <b>August 22, 2007</b>   | <b>EMAIL TO FDA</b>   | <b>ADMINISTRATIVE</b>          |
| <b>September 4, 2007</b> | <b>FAX FROM FDA</b>   | <b>INFORMATION<br/>REQUEST</b> |

***Regulatory Correspondence/Contacts Log***

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|                              |   |                                 |
|------------------------------|---|---------------------------------|
| <b>September 6, 2007</b>     | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>            |
|                              | Submission of information in response to FDA fax of September 4, 2007.                            |                                 |
| <b>September 13, 2007</b>    | <b>FAX FROM FDA</b>   | <b>INFORMATION REQUEST</b>      |
|                              | .   |                                 |
| <b>September 19/20, 2007</b> | <b>TELECONS FROM FDA</b>  | <b>INFORMATION REQUEST</b>      |
| <b>September 20, 2007</b>    | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>            |
|                              | Submission of information in response to FDA fax of September 13, 2007.                           |                                 |
| <b>September 20, 2007</b>    | <b>EMAIL FROM FDA</b>   | <b>INFORMATION REQUEST - PI</b> |
| <b>September 25, 2007</b>    | <b>TELECON TO FDA</b>   | <b>INFORMATION REQUEST</b>      |
| <b>October 1, 2007</b>       | <b>TELECON FROM FDA</b>   | <b>INFORMATION REQUEST</b>      |
| <b>October 2, 2007</b>       | <b>TELECON TO FDA</b>   | <b>INFORMATION REQUEST</b>      |
| <b>October 2, 2007</b>       | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>            |
|                              | Submission of information in response to FDA email of September 20, 2007 requesting PI revisions. |                                 |

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**Regulatory Correspondence/Contacts Log**

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|---------------------------|--|---------------------------------|
| <b>October 4, 2007</b>    | <b>SUBMISSION</b>  | <b>NDA AMENDMENT</b>            |
|                           | Submission of information in response to FDA telecom of October 1, 2007 asking that request for approval of proprietary name be submitted. |                                 |
| <b>October 5, 2007</b>    | <b>TELECON/EMAIL FROM FDA</b>  | <b>INFORMATION REQUEST - PI</b> |
| <b>October 9/10, 2007</b> | <b>TELECON TO FDA</b>  | <b>INFORMATION REQUEST</b>      |
| <b>October 11, 2007</b>   | <b>EMAIL TO FDA</b>  | <b>INFORMATION REQUEST</b>      |
| <b>October 12, 2007</b>   | <b>SUBMISSION</b>  | <b>NDA AMENDMENT</b>            |
|                           | Submission of information in response to FDA email of October 5, 2007 requesting further PI-revisions.                                     |                                 |
| <b>October 16, 2007</b>   | <b>TELECON FROM FDA</b>  | <b>TELECONFERENCE REQUEST</b>   |
| <b>October 17, 2007</b>   | <b>TELECON TO FDA</b>  | <b>TELECONFERENCE REQUEST</b>   |
| <b>October 17, 2007</b>   | <b>EMAIL TO FDA</b>  | <b>TELECONFERENCE REQUEST</b>   |
| <b>October 17, 2007</b>   | <b>SUBMISSION</b>  | <b>NDA AMENDMENT</b>            |
| <b>October 18, 2007</b>   | <b>TELECON FROM FDA</b>  | <b>TELECONFERENCE REQUEST</b>   |
| <b>October 22, 2007</b>   | <b>EMAIL TO FDA</b>  | <b>TELECONFERENCE REQUEST</b>   |

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**Regulatory Correspondence/Contacts Log**

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|                         |                                    |                                   |
|-------------------------|------------------------------------|-----------------------------------|
| <b>October 23, 2007</b> | <b>TELECON FROM FDA</b>            | <b>TELECONFERENCE<br/>REQUEST</b> |
| <b>October 30, 2007</b> | <b>EMAIL TO FDA</b>                | <b>TELECONFERENCE<br/>REQUEST</b> |
| <b>October 31, 2007</b> | <b>TELECONFERENCE<br/>WITH FDA</b> |                                   |
| <b>October 31, 2007</b> | <b>TELECON FROM FDA</b>            | <b>ADMINISTRATIVE</b>             |
| <b>October 31, 2007</b> | <b>EMAIL FROM FDA</b>              | <b>ADMINISTRATIVE</b>             |
| <b>November 2, 2007</b> | <b>TELECON FROM FDA</b>            | <b>CLINICAL</b>                   |
| <b>November 6, 2007</b> | <b>TELECON TO FDA</b>              | <b>CLINICAL</b>                   |
| <b>November 8, 2007</b> | <b>TELECON TO FDA</b>              | <b>CLINICAL</b>                   |
| <b>November 8, 2007</b> | <b>EMAIL TO FDA</b>                | <b>CLINICAL</b>                   |
| <b>November 9, 2007</b> | <b>SUBMISSION</b>                  | <b>NDA AMENDMENT</b>              |

***Regulatory Correspondence/Contacts Log***

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|                          |                                  |                                     |
|--------------------------|----------------------------------|-------------------------------------|
| <b>November 9, 2007</b>  | <b>TELECONS FROM/<br/>TO FDA</b> | <b>CLINICAL</b>                     |
| <b>November 9, 2007</b>  | <b>FAX TO FDA</b>                | <b>CLINICAL</b>                     |
| <b>November 9, 2007</b>  | <b>EMAIL/FAX<br/>FROM FDA</b>    | <b>INFORMATION<br/>REQUEST - PI</b> |
| <b>November 13, 2007</b> | <b>EMAIL TO FDA</b>              | <b>CLINICAL</b>                     |
| <b>November 13, 2007</b> | <b>TELECON TO FDA</b>            | <b>PI REVISIONS</b>                 |
| <b>November 14, 2007</b> | <b>SUBMISSION</b>                | <b>NDA AMENDMENT</b>                |
| <b>November 16, 2007</b> | <b>SUBMISSION</b>                | <b>NDA AMENDMENT</b>                |
| <b>November 26, 2007</b> | <b>SUBMISSION</b>                | <b>NDA AMENDMENT</b>                |
| <b>November 28, 2007</b> | <b>TELECON FROM FDA</b>          | <b>PI REVISIONS</b>                 |
| <b>November 28, 2007</b> | <b>EMAIL TO FDA</b>              | <b>PI REVISIONS</b>                 |
| <b>November 29, 2007</b> | <b>EMAIL FROM FDA</b>            | <b>PI REVISIONS/<br/>CLINICAL</b>   |
| <b>November 29, 2007</b> | <b>TELECONS TO FDA</b>           | <b>PI REVISIONS/<br/>CLINICAL</b>   |

***Regulatory Correspondence/Contacts Log***

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|                             |  |   |
|-----------------------------|--|---|
| <b>November 29/30, 2007</b> | <b>EMAILS TO/FROM FDA</b>              | <b>PI REVISIONS/<br/>CLINICAL</b>   |
| <b>November 30, 2007</b>    | <b>TELECONS/EMAILS<br/>TO/FROM FDA</b> | <b>PEDIATRIC STUDIES</b>  |
| <b>December 3, 2007</b>     | <b>SUBMISSION</b>                      | <b>NDA AMENDMENT</b><br><br>Submission of additional pediatric information as requested by FDA on November 30, 2007.  |
| <b>December 4, 2007</b>     | <b>EMAIL TO FDA</b>                    | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 5, 2007</b>     | <b>TELECON FROM FDA</b>                | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 5, 2007</b>     | <b>EMAIL TO FDA</b>                    | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 5, 2007</b>     | <b>SUBMISSION</b>                      | <b>NDA AMENDMENT</b><br><br>Submission of amendment containing PI revisions and information on PM study/commitment as requested by FDA on November 28-30, 2007. |
| <b>December 7, 2007</b>     | <b>TELECONS TO/FROM<br/>FDA</b>        | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 10, 2007</b>    | <b>TELECONS TO FDA</b>                 | <b>PI REVISIONS<br/>PM STUDY</b>  |

***Regulatory Correspondence/Contacts Log***

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|                             |   |  |
|-----------------------------|---|--|
| <b>December 10, 2007</b>    | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>                   |
|                             | Submission of amendment containing PI revisions requested by FDA on December 7, 2007 and PM commitment.                 |  |
| <b>December 10, 2007</b>    | <b>CORRESPONDENCE<br/>FROM FDA</b>  | <b>PROPRIETARY NAME<br/>ACCEPTANCE</b> |
|                             | FDA forwards letter stating that proprietary name is acceptable. A fax copy of the letter is sent on December 11, 2007. |  |
| <b>December 11-12, 2007</b> | <b>EMAIL TO FDA</b>   | <b>PI REVISIONS<br/>PM STUDY</b>       |
| <b>December 12/13, 2007</b> | <b>TELECON/EMAIL<br/>FROM FDA</b>   | <b>PI REVISIONS<br/>PM STUDY</b>       |
| <b>December 14, 2007</b>    | <b>TELECON FROM FDA</b>   | <b>PEDIATRIC DATA</b>                  |
| <b>December 17, 2007</b>    | <b>EMAIL TO FDA</b>   | <b>PEDIATRIC DATA</b>                  |
| <b>December 17, 2007</b>    | <b>TELECONFERENCE<br/>WITH FDA</b>  | <b>PEDIATRIC DATA</b>                  |
| <b>December 18, 2007</b>    | <b>TELECON TO FDA</b>   | <b>PEDIATRIC DATA</b>                  |
| <b>December 18, 2007</b>    | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>                   |
|                             | Submission of amendment containing proposal for pediatric study, commitment wording and PI revisions.                   |  |
| <b>December 19, 2007</b>    | <b>TELECON TO FDA</b>   | <b>PEDIATRIC DATA</b>                  |

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**Regulatory Correspondence/Contacts Log**

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|                          |                                      |                       |
|--------------------------|--------------------------------------|-----------------------|
| <b>December 20, 2007</b> | <b>TELECON/EMAIL<br/>TO/FROM FDA</b> | <b>PEDIATRIC DATA</b> |
|--------------------------|--------------------------------------|-----------------------|

|                          |                                 |                     |
|--------------------------|---------------------------------|---------------------|
| <b>December 27, 2007</b> | <b>FAX/TELECON<br/>FROM FDA</b> | <b>NDA APPROVAL</b> |
|--------------------------|---------------------------------|---------------------|

|                          |                                    |                     |
|--------------------------|------------------------------------|---------------------|
| <b>December 27, 2007</b> | <b>CORRESPONDENCE<br/>FROM FDA</b> | <b>NDA APPROVAL</b> |
|--------------------------|------------------------------------|---------------------|

NDA approval letter (postmarked December 31, 2007; received January 2, 2008)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentees: Klaus Sommermeyer, Franz Cech, Burghard Weidler, and Klaus Henning  
Patent No: 5,218,108  
Issued: June 8, 1993  
For: HYDROXYLETHYLSTARCH (HES) AS PLASMA EXPANDER AND  
PROCESS FOR PREPARING HES

|                      |  |
|----------------------|--|
| Date: <u>2/21/08</u> | Express Mail Label No. <u>EV214 912 970 US</u> |
|----------------------|--|

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

MAIL STOP HATCH-WAXMAN PTE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

This is an application for extension of patent term under 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.770 and 1.775 for U.S. Patent 5,218,108 ("the '108 Patent").

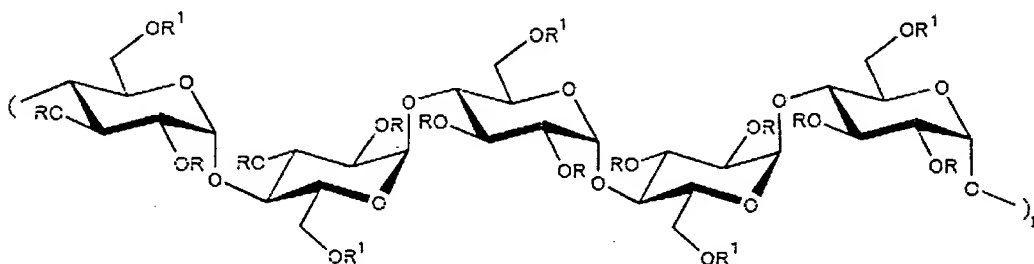
There is one owner of interest in the '108 Patent: Fresenius Kabi (referred to as the "Owner"). Copies of United States Patent and Trademark Office ("US PTO") records as well as additional documents confirming that title resides in the Owner is attached as Exhibit A.

Owner, through the undersigned, represent that it is the owners of record of the '108 Patent and hereby request an extension of the patent term.

The remainder of the sections of this application correspond with subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a).

§1.740(a)(1): *A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.*

The following information is set forth in the package insert or product insert for the approved product. A copy of the Package Insert is included herein as Exhibit B. The brand name of the approved product is VOLUVEN®. The active ingredient of VOLUVEN® is 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection. Hydroxyethyl starch in VOLUVEN® is a synthetic colloid for use in plasma volume replacement. Hydroxyethyl starch is a derivative of thin boiling waxy corn starch, which mainly consists of a glucose polymer (amylopectin) predominately composed of  $\alpha$ -1-4-connected glucose units with several  $\alpha$ -1-6-branches. Substitution of hydroxyethyl groups on the glucose units of the polymer reduces the normal degradation of amylopectin by  $\alpha$ -amylase in the body. The chemical name of the class of hydroxyethyl starch is poly(O-2—hydroxyethyl) starch. The notation "130" in the active ingredient of VOLUVEN® indicates the mean molecular weight of the active ingredient, and specifically indicated that the mean molecular weight is 130,000 Daltons, with a range of 110,000 - 150,000 Daltons. The notation "0.4" indicates a low molar substitution by hydroxyethyl groups of 0.4 (with a range from 0.38 - 0.45) on glucose units of the starch. The low molar substitution (0.4) is the main pharmacological determinant for the beneficial effects of Voluven® on pharmacokinetics, intravascular volume and hemodilution. The pattern of hydroxyethyl substitution ( $C_2/C_6$  ratio) is approximately 9:1. The concentration is 6%. The structural formula of hydroxyethyl starch is, as depicted on the package insert, as follows:



$R = -H, -CH_2CH_2OH$   
 $R^1 = -H, -CH_2CH_2OH$  or glucose units

§1.740(a)(2): *A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.*

Regulatory review occurred under Section 505(i) and 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (Title 21, United States Code Sections 355(i) and 355(b)(2)).

§1.740(a)(3): *An identification of date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.*

VOLUVEN® received approval in a letter dated December 27, 2007. A copy of the approval letter is attached as Exhibit C.

§1.740(a)(4): *In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.*

The sole active ingredient in VOLUVEN® is, as stated above, 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection. No product has been previously approved for commercial marketing or use under the Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act containing this active ingredient alone or in combination. This active ingredient differs from the active ingredients of other hydroxyethyl starch compositions currently available. For example, it is noted that a product Hextend®, containing a high molecular weight hetastarch having high molar substitution, was approved under NDA 20-0952 on March 31, 1999. According to the package insert for Hextend®, the hetastarch component of Hextend® is the same as in the approved Hetastarch Injection products (6% Hetastarch in 0.9% Sodium Chloride Injection). The mean molecular weight of the hetastarch of Hextend® is 670,000 Daltons with a range of 450,000 Daltons to 800,000 Daltons, and the molar substitution of the hetastarch of Hextend® is 0.75. The hydroxyethyl starch of Hextend® thus is

6% hydroxyethyl starch 670/0.75. Because the molecular weights differ so significantly and the molar substitutions also differ, and because of other factors such as branching, the active ingredient of VOLUVEN® differs from the active ingredient of the Hextend® product.

§1.740(a)(5): *A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.740(f) and an identification of the date of the last day on which the application could be submitted.*

This application is being submitted within the sixty day period following the approval of the VOLUVEN® NDA on December 27, 2007. We believe that the last day on which this submission can be made is February 25, 2008.

§1.740(a)(6): *A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.*

U.S. Patent 5,218,108

Inventors: Klaus Sommermeyer, Franz Cech, Burghard Weidler, and Klaus Henning

Issued: June 8, 1993

Filed: June 5, 1990

Date of Expiration: June 8, 2010

§1.740(a)(7): *A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.*

A copy of U.S. Patent 5,218,108, including the entire specification, claims, and drawings, is attached as Exhibit D.

§1.740(a)(8): *A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.*

No disclaimer or reexamination certificate has been issued for the '108 Patent. The first maintenance fee was paid on November 25, 1996; the second maintenance fee was paid on

November 13, 2000, and the third maintenance fee was paid on November 24, 2004. A copy of the USPTO maintenance fee record for this patent is attached as Exhibit E.

§1.740(a)(9): *A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product, if the listed claims include any claim to the approved product; (ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and (iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.*

Claims 1-7 of the '108 Patent are directed to pharmaceutical compositions comprising hydroxyethyl starch. The following chart shows how applicable patent Claims 1 and 2 read on Fresenius' approved product:

| <u>Claim</u>   | <u>Product</u>   |
|--|--|
| 1. Hydroxyethyl starch for use as plasma expander obtainable by hydrolytic pre-degradation of a starch rich in amylopectin, partial hydroxyethylation up to a certain substitution degree in the presence of alkali and subsequent hydrolytic degradation to a certain molecular weight, characterized in that | The approved product contains hydroxyethyl starch for use as a plasma expander, prepared by pre-degrading starch rich in amylopectin, followed by etherification which results in partial hydroxyethylation, and by subsequent hydrolytic degradation. |
| it has a mean molecular weight of 60,000-600,000 and a substitution degree MS of 0.15 to 0.5,  | The approved product has a mean molecular weight within this range, and a substitution degree MS within this range.  |
| the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and  | The approved product has such a ratio within this range.   |
| the substitution degree DS lies in the range from 0.15 to 0.5.   | The approved product has a substitution degree DS within this range.   |

|  |  |
|--|--|
| <p>2. Hydroxyethyl starch according to claim 1, characterized in that it has a mean molecular weight of 80,000 to 400,000 and a substitution degree MS of 0.2-0.4, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.15 to 0.40.</p> | <p>The approved product has these characteristics.</p> |
|--|--|

§1.740(a)(10): *A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:*

*(i) For a patent claiming a human drug, antibiotic, or human biological product:*

*(A) The effective date of the investigational new drug (IND) application and the IND number;*

*(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and*

*(C) The date on which the NDA was approved or the Product License issued.*

- (A) Fresenius Kabi filed an Investigational New Drug (IND) application, BB-IND 9740, ) for hydroxyethyl starch on March 23, 2001, and the FDA indicated that it was received on March 26, 2001, in a letter dated April 5, 2001. A copy of this letter is attached as Exhibit F. The IND has an effective date 30 days after the receipt of the IND, which is April 24, 2001.
- (B) Fresenius Kabi submitted a New Drug Application (NDA) on February 28, 2007, under BN070012.
- (C) The NDA was approved on December 27, 2007, under the existing NDA BN070012 to Fresenius Kabi (Exhibit C).

§1.740(a)(11): *A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.*

Attached as Exhibit G is a chronology briefly describing the significant activities and dates with respect to Fresenius' efforts to seek approval of VOLUVEN®.

§1.740(a)(12): *A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.*

Applicant believes that the '108 Patent is eligible for an extension pursuant to 35 U.S.C. 156(a) and the applicable provisions of 37 C.F.R. 1.710 *et seq.* Using calculations made in accordance with 37 C.F.R. 1.775, the '108 Patent is entitled to a term extension of 1,371 days (the "Term Extension Period"). The Term Extension Period was determined as follows:

#### Length of Regulatory Review Period

Under section 1.775(c), the length of the regulatory review period is 2,439 days, representing the sum of (1) the number of days in the period beginning on the effective date of the IND (April 24, 2001) and ending on the day before the Submission Date of the NDA (February 27, 2007) (2,136 days) and (2) the number of days in the period beginning on the Submission Date of the NDA (February 28, 2007) and ending on the date that the Product's NDA was approved (December 27, 2007) (303 days).

#### Length of Patent Term Extension

Under 1.775(d), a total of 1,068 days were subtracted from the 2,439 day length of the Regulatory Review Period, as follows:

- (i) 0 days were prior to the date on which the '108 Patent issued;
- (ii) 0 days during which the applicant did not act with due diligence; and
- (iii) 1,068 days representing one-half the number of days (2,136 days) remaining in the period defined by paragraph (c)(1) after which a total of 0 days were subtracted in accordance with paragraphs (d)(1)(i) and (d)(1)(ii).

Thus, the period calculated under section 1.775(d)(1) is 1,371 days.

The period calculated under section 1.775(d)(2), by adding 1,371 days to the original expiration date of the '108 patent (July 8, 2010), ends on April 9, 2014.

The period calculated under section 1.775(d)(3), by adding 14 years to the date of approval of the application under section 505 of the Federal Food Drug and Cosmetics Act, ends on December 27, 2021.

The date selected under section 1.775(d)(4), by comparing the two dates and selecting the earlier, is April 9, 2014.

Because the '108 Patent issued after September 24, 1984, the date determined under section 1.775(d)(5) is arrived at by adding 5 years to the original expiration date of the '108 Patent (July 8, 2015), and comparing that date (July 8, 2015) to the date determined under section 1.775(d)(4), results in selection of April 9, 2014 as the earlier date and thus the date to which the term of the '108 Patent should be extended.

§1.740(a)(13): *A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.*

Applicant, through the undersigned representative, hereby acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

§1.740(a)(14): *The prescribed fee for receiving and acting upon the application for extension.*

The prescribed fee for receiving and acting upon this application is \$1,120.00. A check in this amount is submitted with this application. Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 08-0380. A copy of this letter is enclosed for accounting purposes.

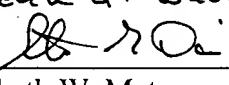
§1.740(a)(15): *The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.*

Please direct all inquiries and correspondence relating to this application for patent term extension to:

Brian T. Moriarty, Esq.  
Elizabeth W. Mata, Esq.  
Customer No.: 021005  
Hamilton, Brook, Smith & Reynolds, P.C.  
530 Virginia Road  
P.O. Box 9133  
Concord, MA 01742  
Tel: (978) 341-0036

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

Steven G. Davis for Elizabeth W. Mata  
By  Registration No. 38,652  
Elizabeth W. Mata  
Registration No. 38,236  
Telephone: (978) 341-0036  
Facsimile: (978) 341-0136

Concord, MA 01742-9133  
Dated: February 21, 2008

SCHEDULE OF EXHIBITS

|           |  |
|-----------|--|
| Exhibit A | Ownership Records  |
| Exhibit B | Package Insert   |
| Exhibit C | Approval Letter dated December 27, 2007                    |
| Exhibit D | U.S. Patent No. 5,218,108                                  |
| Exhibit E | USPTO Maintenance Fee Record for U.S. Patent No. 5,218,108 |
| Exhibit F | Document Indicating Commencement of Phase III Trial        |
| Exhibit G | Chronology regarding VOLUVEN®                              |

Exhibit A:

1. Copy of executed assignment from inventors Klaus Sommermeyer, Franz Cech, Burghard Weidler, and Klaus Henning to Fresenius Aktiengesellschaft (AKA Fresenius AG), recorded in the United States Patent and Trademark Office on Reel 005345, Frames 0989 through 0992.
2. Copy of executed confirmatory assignment from Fresenius Aktiengesellschaft to Fresenius Kabi Deutschland GmbH (AKA Fresenius Kabi)

ASSIGNMENT

464 533234 TR 1924

WHEREAS, We Dr. K. Sommermeyer,  
Dr. F. Cech, Dr. K. Henning and Dr. B. Weidler, are the joint inventors of \_\_\_\_\_,  
\_\_\_\_\_, application for United States Letters Patent  
which is executed of even date herewith; and

WHEREAS, FRESENIUS AG, D-6380 Bad Homburg v.d.H., a  
corporation created and existing under and by virtue of the laws of the  
State and/or Country of the Federal Republik of Germany, is  
desirous of acquiring the entire right, title and interest in and to the  
aforesaid invention throughout the world, and all right, title and  
interest in, to and under any and all Letters Patent of the United States  
and all other countries throughout the world;

NOW, THEREFORE, for and in consideration of the sum of One Dollar  
(\$1.00) to us in hand paid by FRESENIUS AG  
and for other good and valuable considerations, the receipt of which is  
hereby acknowledged, we hereby sell, assign, transfer and set over to  
FRESENIUS AG, all right, title and  
interest in and to the said invention throughout the world, and said  
application for U.S. Letters Patent, and any and all divisions,  
continuations, and reissues thereof, and any and all Letters Patent of  
the United States and foreign countries which may be granted therefor,  
the same to be held and enjoyed by FRESENIUS AG  
\_\_\_\_\_ for its own use and benefit, and for the  
use and benefit of its successors, assigns, or other legal  
representatives, to the end of the term or terms for which said Letters  
Patent of the United States or foreign countries are or may be granted or  
reissued, as fully and entirely as the same would have been held and  
enjoyed by us if this assignment and sale had not been made.

And we hereby authorize and request the Commissioner of Patents and  
Trademarks to issue any and all Letters Patent of the United States on  
said invention or resulting from said application and from any and all  
divisions, continuations, and reissues thereof, to FRESENIUS AG

REF 5345 FRAME 990

\_\_\_\_\_, as assignee of our entire interest, and hereby covenant that we have the full right to convey the entire interest herein assigned, and that we have not executed and will not execute any agreement in conflict herewith.

And we further hereby covenant and agree that we will, at any time, upon request, execute and deliver any and all papers that may be necessary or desirable to perfect the title of said invention and to such Letters Patent as may be granted therefor, to FRESENIUS AG

\_\_\_\_\_, its successors, assigns, or other legal representatives and that if FRESENIUS AG

\_\_\_\_\_, its successors, assigns or other legal representatives shall desire to file any divisional or continuation applications or to secure a reissue of such Letters Patent, or to file a disclaimer relating thereto, will upon request, sign all papers, make all rightful oaths and do all lawful acts requisite for the filing of such divisional or continuation application, or such application for reissue and the procuring thereof, and for the filing of such disclaimer, without further compensation but at the expense of said assignee, its successors, or other legal representatives.

And we do further covenant and agree that we will, at any time upon request, communicate to FRESENIUS AG, its successors, assigns or other legal representatives, such facts relating to said invention and Letters Patent or the file history thereof as may be known to me, and testify as to the same in any interference or other litigation when requested so to do, without further compensation but at the expense of said assignee, its successors, or other legal representatives.

EXECUTED THIS 25 day of April, 1990.

Signature \_\_\_\_\_

Dr. K. Sommermeier

EXECUTED THIS 25 day of April, 1990.

Signature \_\_\_\_\_

Dr. F. Cech

REEL 5345 FRAME 991

EXECUTED THIS 26 day of April, 1990.

Signature X

Dr. B. Weidler

EXECUTED THIS 25 day of April, 1990.

Signature Ula, Henning

Dr. K. Henning

REF 5345 FR 992

RECORDED  
PATENT AND TRADEMARK  
OFFICE

JUN 5 1990

CONFIRMATORY ASSIGNMENT

Whereas, by virtue of an Assignment recorded in the United States Patent and Trademark Office on Reel 005345, Frames 0989 through 0992, Fresenius Aktiengesellschaft (hereinafter "Assignor") of Else-Kroener-Strasse 1, 61352 Bad Homburg v.d.H., Germany, was the owner of United States Letters Patent No. 5,218,108, issued June 8, 1993 (hereinafter "Patent").

Whereas, Fresenius Kabi Deutschland GmbH (hereinafter "Assignee"), a German corporation, of Else-Kroener-Strasse 1, 61352 Bad Homburg v.d.H., Germany, was desirous of acquiring from Assignor, an interest in, to and under the aforesaid Patent and the invention therein described and claimed, and in accordance with an agreement executed June 9, 1999 (hereinafter "Agreement"), Assignee acquired from Assignor all of its right, title and interest in the Patent in return for certain obligations to Assignor.

Now, therefore, Assignor hereby confirms that for good and valuable consideration, the receipt of which was hereby acknowledged in the Agreement, it has sold, transferred and conveyed to Assignee its entire right, title and interest in, to and under said Patent, to the full end of the term for which Letters Patent were granted, and any continuations, reissues, or extensions thereof and the invention therein described and claimed, including all claims, if any, which may have arisen for infringement of the Patent prior to the date of this confirmatory assignment.

Assignor further agrees that Assignor will, without demanding any further consideration therefor, at the request but at the expense of Assignee, do all lawful and just acts, including the execution and acknowledgment of instruments, that may be or become necessary for obtaining, sustaining, or reissuing the Patent, and for maintaining and perfecting Assignee's right, its

Docket No. [ ]

successors, assigns and legal representatives, to the Patent and any continuations, reissues or extensions thereof, and preliminary or other statements and the giving of testimony in any interference or other proceeding in which said invention or any application or patent directed thereto may be involved.

Fresenius Aktiengesellschaft

By B. Staude

Print Name: I.V. Elgit Staude  
Patent Manager

Title

Date February 18, 2008

Witness Signature S. Calabrò - Folchert

Print Witness Name I.V. Dr. Silvana Calabrò-Folchert  
Patent Manager

Address Fröderstr. 41

35428 Langgöns

Witness Signature [Signature]

Print Witness Name Stefan Weiß

Address Hofedeweg 1

60320 Frankfurt

## NON ANNOTATED VERSION

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Voluven<sup>®</sup> safely and effectively. See full prescribing information for Voluven<sup>®</sup>.

**Voluven<sup>®</sup> (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection)**

**For administration by intravenous infusion.**

**Initial U.S. Approval: To be determined**

### INDICATIONS AND USAGE

Voluven<sup>®</sup> is a plasma volume substitute indicated for the treatment and prophylaxis of hypovolemia. (1)

### DOSAGE AND ADMINISTRATION

**Administer by intravenous infusion only.**

- Daily dose and rate of infusion depend on the patient's blood loss, hemodynamics and on the hemodilution effects. (2)
- Initiate infusion slowly due to possible anaphylactoid reactions (2, 5.1)
- See full prescribing information for pediatric administration (2.2, 8.4)

### DOSAGE FORMS AND STRENGTHS

500 mL *freeflex*<sup>®</sup> flexible plastic intravenous solution container. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection. (3)

### CONTRAINDICATIONS

- Known hypersensitivity to hydroxyethyl starch (4)
- Fluid overload e.g., pulmonary edema and congestive heart failure (4)
- Renal failure with oliguria or anuria not related to hypovolemia (4)
- Patients receiving dialysis (4)
- Severe hyponatremia or severe hyperchloremia (4)
- Intracranial bleeding (4)

### WARNINGS AND PRECAUTIONS

- Anaphylactoid and hypersensitivity reactions (5.1, 6)
- Avoid fluid overload; adjust dosage in patients with cardiac or renal dysfunction (5.1)
- In severe dehydration, a crystalloid solution should be given first (5.1)
- Observe caution in patients with severe liver disease or bleeding disorders (5.1)
- Monitor kidney function, fluid balance and serum electrolytes (5.2)
- Elevated serum amylase values may occur and interfere with the diagnosis of pancreatitis (5.3)
- High dosages may cause dilution of blood components (5.3)

#### **-----ADVERSE REACTIONS-----**

Anaphylactoid/hypersensitivity reactions can occur. Most common adverse reactions (incidence >1%) are pruritus, elevated serum amylase, hemodilution (resulting in dilution of blood components, e.g., coagulation factors and other plasma proteins, and in a decrease in hematocrit). (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Hospira Inc. at 1-800-441-4100 or electronically at [ProductComplaintsPP@hospira.com](mailto:ProductComplaintsPP@hospira.com) or FDA at 1-800-FDA-1088 or electronically at [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### **-----DRUG INTERACTIONS-----**

No interactions with other drugs or nutritional products are known. (7)  
The safety and compatibility of additives have not been established.

#### **-----USE IN SPECIFIC POPULATIONS-----**

- Pediatric patients: Dosage should be adjusted to individual patient needs. (2.2, 8.4)
- Renal impaired or geriatric patients: Use care in dosage selection. (8.6)

**After reviewing the Highlights section, please read the following full prescribing information for this drug.**

See 17 for PATIENT COUNSELING INFORMATION  
**Labeling Revision Date:** TBD

*Draft: 2007/12/18*

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## **FULL PRESCRIBING INFORMATION: CONTENTS\***

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\*Sections of subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) is indicated for the treatment and prophylaxis of hypovolemia.

It is not a substitute for red blood cells or coagulation factors in plasma.

### 2 DOSAGE AND ADMINISTRATION

Voluven® is administered by intravenous infusion only. The daily dose and rate of infusion depend on the patient's blood loss, on the maintenance or restoration of hemodynamics and on the hemodilution (dilution effect). Voluven® can be administered repetitively over several days. [see *Warnings and Precautions* (5)]

The initial 10 to 20 mL should be infused slowly, keeping the patient under close observation due to possible anaphylactoid reactions. [see *General Warnings and Precautions* (5.1)]

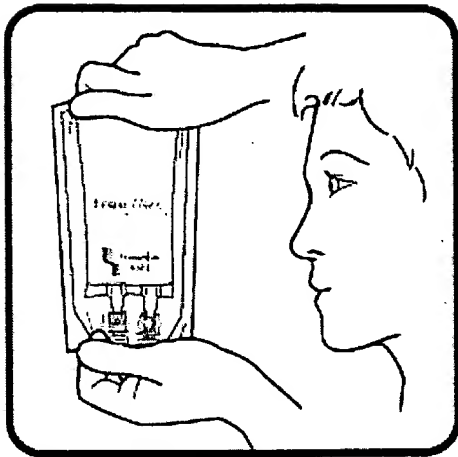
#### 2.1 Adult Dose

Up to 50 mL of Voluven® per kg of body weight per day (equivalent to 3 g hydroxyethyl starch and 7.7 mEq sodium per kg of body weight). This dose is equivalent to 3500 mL of Voluven® for a 70 kg patient.

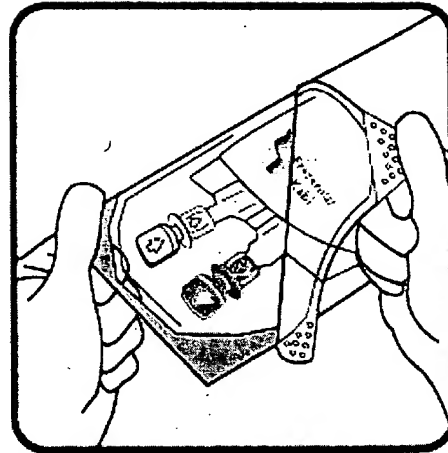
#### 2.2 Pediatric Dose

Limited clinical data on the use of Voluven® in children are available. In 41 children including newborns to infants (< 2 years), a mean dose of  $16 \pm 9$  mL/kg was administered. The dosage in children should be adapted to the individual patient colloid needs, taking into account the disease state, as well as the hemodynamic and hydration status. The safety and efficacy of Voluven® have not been established in the age group of 2 to 12 years. Use of Voluven® in children > 12 years is supported by evidence from adequate and well-controlled studies of Voluven® in adults and by data from children < 2 years old. [see *Pediatric Use* (8.4)]

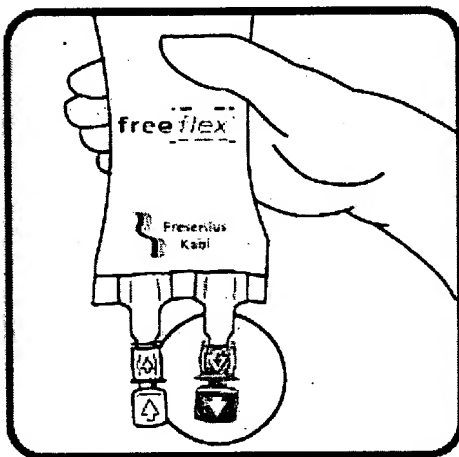
#### 2.3 Directions for Use of Voluven®



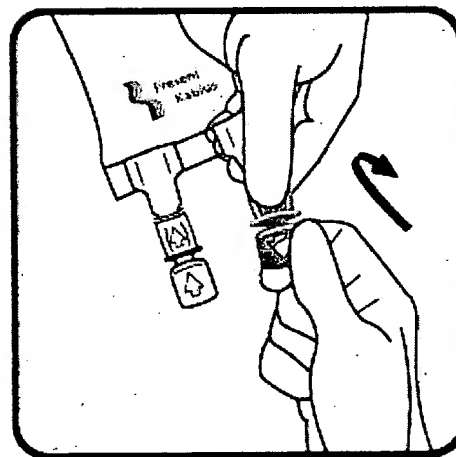
- Check the solution composition, lot number and expiry date, inspect the container for damage or leakage, if damaged do not use.



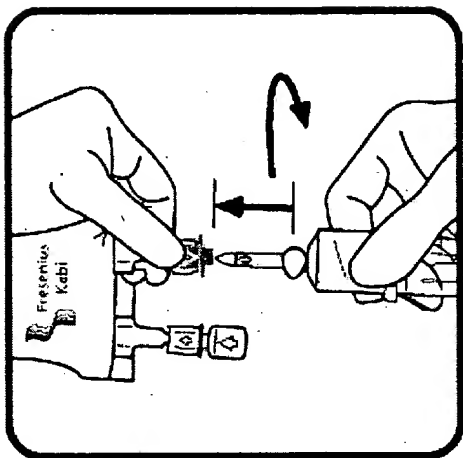
- Use opening aid to remove over-wrap.



- Identify the blue infusion (administration) port.



- Break off the blue tamper-evident cover from the **freeflex**® infusion port.



- Hang the bag on the infusion stand. Press drip chamber to get fluid level. Prime infusion set. Connect and adjust the flow rate.

- Close roller clamp. Insert the spike until the clear plastic collar of the port meets the shoulder of the spike.
  - Use a non-vented standard infusion set and close air inlet.
1. Do not remove the **freeflex**<sup>®</sup> IV container from its overwrap until immediately before use.
  2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
  3. Do not administer unless the solution is clear, free from particles and the **freeflex**<sup>®</sup> IV container is undamaged.
  4. Voluven<sup>®</sup> should be used immediately after insertion of the administration set.
  5. Do not vent.
  6. If administered by pressure infusion, air should be withdrawn or expelled from the bag through the medication/administration port prior to infusion.
  7. Discontinue the infusion if an adverse reaction occurs.
  8. It is recommended that administration sets be changed at least once every 24 hours.
  9. For single use only. Discard unused portion.

### **INCOMPATIBILITIES**

The safety and compatibility of additives have not been established.

### **3 DOSAGE FORMS AND STRENGTHS**

500 mL **freeflex**<sup>®</sup> flexible plastic intravenous solution container are available. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection.

#### **4 CONTRAINDICATIONS**

The use of Voluven<sup>®</sup> is contraindicated in the following conditions:

- known hypersensitivity to hydroxyethyl starch [see *General Warnings and Precautions (5.1)*]
- fluid overload (hyperhydration) and especially in cases of pulmonary edema and congestive heart failure
- renal failure with oliguria or anuria not related to hypovolemia
- patients receiving dialysis treatment
- severe hyponatremia or severe hyperchloremia
- intracranial bleeding.

#### **5 WARNINGS AND PRECAUTIONS**

##### **5.1 General Warnings and Precautions**

Anaphylactoid reactions (mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema) have been reported with solutions containing hydroxyethyl starch. If a hypersensitivity reaction occurs, administration of the drug should be discontinued immediately and the appropriate treatment and supportive measures should be undertaken until symptoms have resolved. [see *Adverse Reactions (6)*]

Fluid status and rate of infusion should be assessed regularly during treatment, especially in patients with cardiac insufficiency or severe kidney dysfunction.

In cases of severe dehydration, a crystalloid solution should be given first. Generally, sufficient fluid should be administered in order to avoid dehydration.

Caution should be observed before administering Voluven<sup>®</sup> to patients with severe liver disease or severe bleeding disorders (e.g., severe cases of von Willebrand's disease).

##### **5.2 Monitoring: Laboratory Tests**

Clinical evaluation and periodic laboratory determinations are necessary to monitor fluid balance, electrolyte concentrations, kidney function, acid-base balance, and coagulation parameters during prolonged parenteral therapy or whenever the patient's condition warrants such evaluation.

##### **5.3 Interference with Laboratory Tests**

Elevated serum amylase levels may be observed temporarily following administration of the product and can interfere with the diagnosis of pancreatitis.

At high dosages the dilutional effects may result in decreased levels of coagulation factors and other plasma proteins and a decrease in hematocrit.

## 6 ADVERSE REACTIONS

### 6.1 Overall Adverse Reaction Profile

From the accumulated clinical development experience, expected adverse reactions after administration of Voluven® occurring in less than 10% of patients are as follows:

*Immune system disorders (Rare, >0.01% to <0.1%):* Products containing hydroxyethyl starch may lead to anaphylactoid reactions (hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema). In the event of an intolerance reaction, the infusion should be discontinued immediately and the appropriate emergency medical treatment initiated. [see *General Warnings and Precautions (5.1)*]

*Skin and subcutaneous tissue disorders (Common, >1 to <10%, dose dependent):* Prolonged administration of high dosages of hydroxyethyl starch may cause pruritus (itching) which is an undesirable effect observed with all hydroxyethyl starches.

*Investigations (Common, >1% to <10%, dose dependent):* The concentration of serum amylase can rise during administration of hydroxyethyl starch and can confound the diagnosis of pancreatitis. At high doses the dilutional effects may result in decreased levels of coagulation factors and other plasma proteins and in a decrease of hematocrit. [see *Interference with Laboratory Tests (5.3)*]

### 6.2 Adverse Reactions in Clinical Trials

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug may not reflect the rates observed in practice.

During clinical development, 471 patients were exposed to Voluven®, and a total of 768 patients received the hydroxyethyl starch 130/0.4 drug substance contained in Voluven® at different concentrations (2%, 4%, 6%, or 10%) and at cumulative doses of several mL up to 66 L<sup>1)</sup>. The mean duration of treatment with hydroxyethyl starch 130/0.4 was  $3.9 \pm 3.3$  days, mean cumulative doses were  $3338 \pm 3695$  mL, and the longest follow-up period was 90 days.

In the US trial, 100 patients undergoing elective orthopedic surgery were treated either with Voluven® (N=49) or hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) (N=51) for intraoperative volume replacement. Mean infusion volumes were  $1613 \pm 778$  mL for Voluven® and  $1584 \pm 958$  mL for hetastarch.

*Adverse reactions observed in at least 1% of patients:* In the US trial comparing Voluven® with hetastarch, a possible relationship to Voluven® was reported in five cases in a total of three patients (aPTT elevated, PT prolonged, wound hemorrhage, anemia, pruritus). A possible relationship to hetastarch was reported in five patients (three cases of coagulopathy; two cases of pruritus). The three coagulopathy cases in the hetastarch group were serious and occurred in patients receiving more than the labeled ceiling dose (20 mL/kg), whereas no serious coagulopathy occurred in the Voluven® group.

### **6.3 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of Voluven® and other types of hydroxyethyl starch solutions. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The safety profile from postmarketing experience of Voluven® is not different from the profile obtained from clinical trials performed using the product.

Based on spontaneous reporting of hypersensitivity reactions, urticaria, bronchospasm, or hypotension were the most frequently reported serious adverse drug reactions for patients treated with Voluven®.

With the administration of hydroxyethyl starch solutions, disturbances of blood coagulation can occur depending on the dosage<sup>2)</sup>.

## **7 DRUG INTERACTIONS**

No interactions with other drugs or nutritional products are known.

The safety and compatibility of other additives have not been established [see *Directions for Use of Voluven®* (2.3)].

## **8 USE IN SPECIAL POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C. Voluven® has been shown to cause embryocidal or other adverse effects in rats and rabbits when given in doses 1.7 times the human dose. There are no adequate and well-controlled studies in pregnant women. Voluven® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The type of hydroxyethyl starch present in Voluven® had no teratogenic properties in rats or rabbits. At 5 g/kg of body weight per day, administered as a bolus injection, fetal retardations and embryo-lethal effects were observed in rats and rabbits, respectively. In rats, a bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. All adverse effects were seen exclusively at maternal toxic doses due to fluid overload. [see *Toxicology* (13.2.1)]

Fertility studies on directly exposed animals have not been conducted.

### **8.2 Labor and Delivery**

Information on the use of Voluven® during labor or delivery is unknown.

### **8.3 Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Voluven® is administered to a nursing woman.

### **8.4 Pediatric Use**

In one trial, children including newborns to infants (< 2 years) undergoing elective surgery were randomized to receive Voluven® (N=41) or 5% albumin (N=41). The mean dose of Voluven® administered was  $16 \pm 9$  mL/kg<sup>3)</sup>.

Voluven® may be given to premature infants and newborns only after a careful risk/benefit evaluation. The safety and efficacy of Voluven® have not been established in the age group of 2 to 12 years. Use of Voluven® in children > 12 years is supported by evidence from adequate and well-controlled studies of Voluven® in adults and by data from children < 2 years old. Dosage in children should be adapted to individual patient colloid needs, taking into account underlying disease, hemodynamics and hydration status. [see *Pediatric Dose* (2.2)]

#### **8.5 Geriatric Use**

Of the total number of subjects in clinical studies of Voluven® (N= 471), 32% were 65 years old and older while 7% were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

#### **8.6 Renal impairment**

Voluven® is mainly excreted by the kidneys, and the risk of adverse reactions may be greater in patients with impaired renal function. Volume status, infusion rate, and urine output should be closely monitored. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. [see *Pharmacokinetics* (12.3)]

### **9 DRUG ABUSE AND DEPENDENCE**

Voluven® is not considered to be a drug of abuse potential.

### **10 OVERDOSAGE**

As with all plasma volume substitutes, overdosage can lead to overloading of the circulatory system (e.g. pulmonary edema). In this case, the infusion should be stopped immediately and if necessary, a diuretic should be administered. [see *General Warnings and Precautions* (5.1)]

### **11 DESCRIPTION**

Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) is a clear to slightly opalescent, colorless to slightly yellow, sterile, non-pyrogenic, isotonic solution for intravenous administration using sterile equipment.

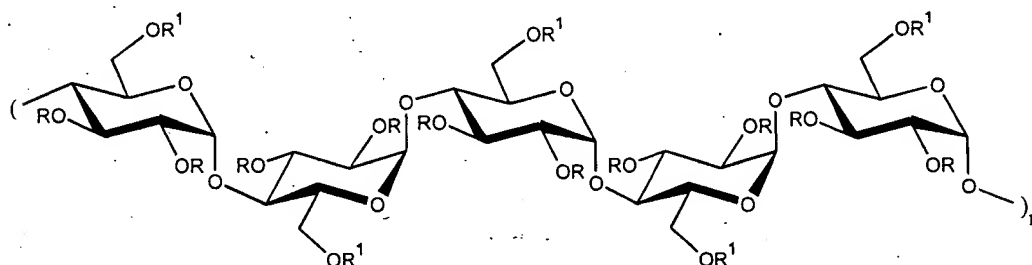
Each 100 mL of the solution contains:

|                             |        |
|-----------------------------|--------|
| Hydroxyethyl Starch 130/0.4 | 6 g    |
| Sodium Chloride USP         | 900 mg |
| in Water for Injection USP  |        |

pH adjusted with Sodium Hydroxide USP  
or Hydrochloric Acid USP

Electrolytes (mEq/L): Sodium 154, Chloride 154. pH 4 to 5.5. Calculated osmolarity 308 mOsmol/L.

The hydroxyethyl starch contained in Voluven® is a synthetic colloid for use in plasma volume replacement. The chemical name of hydroxyethyl starch is poly(O-2-hydroxyethyl) starch. The structural formula of hydroxyethyl starch is



R = -H, -CH<sub>2</sub>CH<sub>2</sub>OH  
R<sup>1</sup> = -H, -CH<sub>2</sub>CH<sub>2</sub>OH or glucose units

Voluven® is packaged in 500 mL flexible plastic containers (**freeflex**®). **Freeflex**® is a flexible container made from coextruded polyolefin and is free of PVC, plasticizers, adhesives or latex (Non-DEHP, Latex-free). The **freeflex**® container offers an air-closed system and can be used with non-vented IV sets which prevent external air contamination. **Freeflex**® is collapsible and can be used in emergency cases for pressure infusion.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Voluven® contains hydroxyethyl starch in a colloidal solution which expands plasma volume when administered intravenously. This effect depends on the mean molecular weight (130,000 daltons; range 110,000 – 150,000 daltons), the molar substitution by hydroxyethyl groups (0.4; range 0.38 – 0.45) on glucose units of the starch, the pattern of hydroxyethyl substitution (C<sub>2</sub>/C<sub>6</sub> ratio) of approximately 9:1, and the concentration (6%), as well as the dosage and infusion rate.

Hydroxyethyl starch is a derivative of thin boiling waxy corn starch, which mainly consists of a glucose polymer (amylopectin) predominately composed of α-1-4-connected glucose units with several α-1-6-branches. Substitution of hydroxyethyl groups on the glucose units of the polymer reduces the normal degradation of amylopectin by α-amylase in the body. The low molar substitution (0.4) is the main pharmacological determinant for the beneficial effects of Voluven® on pharmacokinetics, intravascular volume and hemodilution<sup>4)</sup>. To describe the molecular weight and molar substitution characteristics of the hydroxyethyl starch in Voluven®, the compound is designated as hydroxyethyl starch 130/0.4.

## 12.2 Pharmacodynamics

After isovolemic exchange of blood with 500 mL of Voluven® in healthy volunteers, blood volume is maintained for at least 6 hours.

## 12.3 Pharmacokinetics

The pharmacokinetic profile of hydroxyethyl starch is complex and largely dependent on its molar substitution as well as its molecular weight<sup>4)</sup>. When administered intravenously, molecules smaller than the renal threshold (60,000-70,000 daltons) are readily and rapidly excreted in the urine, while molecules with higher molecular weights are metabolized by plasma  $\alpha$ -amylase prior to excretion via the renal route.

The mean *in vivo* molecular weight of Voluven® in plasma is 70,000 – 80,000 daltons immediately following infusion and remains above the renal threshold throughout the treatment period.

Following intravenous administration of 500 mL Voluven® to healthy volunteers, plasma levels of Voluven® remain at 75% of peak concentration at 30 minutes post-infusion and decrease to 14% at 6 hours post-infusion. Plasma levels of Voluven® return to baseline levels 24 hours following infusion. Plasma clearance, volume of distribution, and elimination half-life of Voluven® in healthy volunteers following IV administration of 500 mL were 31.4 mL/min, 5.9 liters, and 12 hours, respectively. Approximately 62 % of Voluven® was excreted as hydroxyethyl starch molecules in urine within 72 hours.

The pharmacokinetics of Voluven® are similar following single and multiple dose administration. No significant plasma accumulation occurred after daily administration of 500 mL of a 10% solution containing hydroxyethyl starch 130/0.4 over a period of 10 days. Approximately 70% of Voluven was excreted as hydroxyethyl starch molecules in urine within 72 hours.

### Renal Impairment:

Following a single intravenous administration of Voluven® (500 mL) in subjects with varying degrees of renal dysfunction, the AUC and clearance of Voluven® increased by 73% and decreased by 42% in patients, respectively, with creatinine clearance <50 mL/min as compared to patients with creatinine clearance >50 mL/min. However, terminal half-life and peak hydroxyethyl starch concentration were not affected by renal impairment. Plasma levels of Voluven® returned to baseline levels 24 hours following infusion. Approximately 59 % and 51 % of Voluven® were excreted as hydroxyethyl starch molecules in urine within 72 hours in patients with creatinine clearance  $\geq 30$  mL/min and <30 mL/min, respectively.

There are no data available on the use of Voluven® in patients undergoing hemodialysis.

Pharmacokinetic data in patients with hepatic insufficiency or in pediatric or geriatric patients are not available. Effects of gender or race on the pharmacokinetics of Voluven® have not been studied.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals to evaluate the carcinogenic potential of Voluven® have not been performed. No mutagenic effects were observed with hydroxyethyl starch 130/0.4 10% solution in the following tests on mutagenic activity: *Salmonella typhimurium* reverse mutation assay (*in vitro*), mammalian cells in the *in vitro* gene mutation assay, assessment of the clastogenic activity in cultured human peripheral lymphocytes (*in vitro*), bone marrow cytogenetic test in Sprague-Dawley rats.

Fertility studies on directly exposed animals have not been performed.

### **13.2 Animal Toxicology and Pharmacology**

#### **13.2.1 Toxicology**

Three-month repeat infusion toxicology studies were conducted in rats and dogs in which three groups of animals were administered daily intravenous infusion over three hours. Dosing volumes of either 60 or 90 mL/kg body weight of hydroxyethyl starch 130/0.4 (10% solution) or 90 mL/kg 0.9% sodium chloride injection were studied. Observed toxicity following repeat infusion of hydroxyethyl starch is consistent with the oncotic properties of the solution resulting in hypervolemia in the animals. There were no apparent gender-related effects on toxicity following repeat administration of hydroxyethyl starch 130/0.4 in rats or dogs.

In reproduction studies in rats and rabbits, hydroxyethyl starch 130/0.4 (10% solution) had no teratogenic properties. Embryo-lethal effects were observed in rabbits at 5 g/kg body weight/day. In rats, bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. Signs of fluid overload were seen in the dams. Hydroxyethyl starch 130/0.4 (10% solution) was observed to have no effect in studies assessing skin sensitization, antigenicity, and blood compatibility.

#### **13.2.2 Pharmacology**

The pharmacodynamic effect of Voluven® was examined in a hemorrhagic shock model in conscious rats and a hemodilution model in dogs. In both studies the control group received pentastarch (6% hydroxyethyl starch 200/0.5).

Voluven® was as effective as pentastarch in maintaining cardiopulmonary function during isovolemic hemodilution in beagle dogs. In the three-hour follow-up period no additional administration of colloid was necessary.

There were no differences in long-term survival of rats after a single administration of Voluven® and pentastarch solutions following induced hemorrhagic shock (67% and 50% blood loss). In the 67% induced bleeding group receiving Voluven® (N=6), the survival rate was 83% which is within the normal range for this type of experiment. In the corresponding pentastarch group, survival was 100%. Infusion of Ringer's lactate resulted in a 50% survival rate after a 50% blood loss and a 0% survival after a 67% blood loss.

After multiple intravenous infusions of 0.7 g per kg body weight per day of 10% hydroxyethyl starch 130/0.4 or 10% hydroxyethyl starch 200/0.5 solution during 18 consecutive days, the plasma hydroxyethyl starch concentration in rats treated with hydroxyethyl starch 130/0.4 was lower compared to rats treated with hydroxyethyl starch 200/0.5. Hydroxyethyl starch 130/0.4 was eliminated faster than hydroxyethyl starch 200/0.5. In both groups, clear signs of hydroxyethyl starch tissue storage were detected in lymph nodes and spleen. Numerous empty vacuoles in macrophages were observed. Only minimal cellular vacuolization was found in the liver and kidney. Histochemical differences between the groups were not observed.

A study with 10% radiolabeled <sup>14</sup>C-hydroxyethyl starch 130/0.4 and 10% <sup>14</sup>C-hydroxyethyl starch 200/0.5 solutions was carried out<sup>6)</sup>. In animals treated with hydroxyethyl starch 130/0.4, radioactivity decreased from 4.3% of the total administered dose (2.6 g hydroxyethyl starch 130/0.4 per animal) on day 3 to 0.65% on day 52. In animals treated with hydroxyethyl starch 200/0.5, the <sup>14</sup>C-activity decreased from 7.7% of the total administered dose (2.7 g hydroxyethyl starch 200/0.5 per animal) on day 3 to 2.45% on day 52. These results confirm the faster elimination and lower persistence of hydroxyethyl starch 130/0.4 in tissue.

## 14 CLINICAL STUDIES

Voluven® was studied in controlled clinical trials in adult and pediatric surgical patients and in patients in intensive care units. Clinical studies included patients undergoing various types of surgery (orthopedic, urologic, cardiac) and trauma intensive care for situations in which hypovolemia is treated (pre-, intra-, and postoperative) or prevented (autologous blood donation, acute normovolemic hemodilution, hypervolemic hemodilution before cardiac surgery). The safety and efficacy of Voluven® were compared to other colloidal plasma substitutes [pentastarch (6% hydroxyethyl starch 200/0.5), hetastarch (6% hydroxyethyl starch 450/0.7), gelatin solution or human serum albumin] in studies carried out in common clinical settings of volume replacement therapy. Perioperative fluid administration of Voluven® ranged from 500 to 4500 mL/day in surgical patients, and cumulatively, 6 to 66 L during stays in intensive care units following traumatic brain injury.

A prospective, controlled, randomized, double-blind, multi-center trial of 100 patients undergoing elective orthopedic surgery was conducted in the US evaluating Voluven® (N=49) compared to hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) (N=51) for intraoperative volume replacement therapy<sup>7)</sup>. The primary efficacy variable, total volume of colloid solution required for intraoperative volume replacement therapy, was equivalent for the two treatment groups. Mean volume infused was 1613 ± 778 mL for Voluven® and 1584 ± 958.4 mL for hetastarch. The ratio Voluven®/hetastarch was estimated as 1.024 with a 95%

confidence interval (0.84, 1.25), which was included within the equivalence range of (0.55, 1.82) prespecified in the study protocol. This indicated that Voluven® and hetastarch have similar efficacy as intraoperative volume replacement therapy in major orthopedic surgery.

A second objective of the trial was to show superiority for safety between Voluven® and hetastarch. Four safety endpoints were prospectively defined and compared in a sequential manner (in order to preserve the type-I error rate, i.e., observing a difference where none actually exists). Per protocol, if there was no difference found between treatment arms for the first safety endpoint (EBL), the remaining endpoints were to be considered exploratory analyses requiring additional studies for confirmation.

Overall, no significant differences in serious adverse events were noted between the two treatment arms, but three cases of serious coagulopathy occurred in the hetastarch treatment arm. All three subjects received high doses (>3000 mL; labeled ceiling dose = 20 mL/Kg) of the product, which are known to increase the risk of bleeding. Since EBL for the two treatment arms was not statistically different (95% confidence interval includes unity), the difference observed for Factor VIII (see table, below) must be interpreted with caution. An exploratory analysis of total erythrocyte volume transfused (8.0 mL/kg vs. 13.8 mL/kg, Voluven® vs hetastarch, respectively) must also be viewed with caution.

**Table: Safety Variables for Study HS-13-30-US**

| Variable                           | Mean            |                    | Ratio VOLUVEN/Hetastarch |                |
|------------------------------------|-----------------|--------------------|--------------------------|----------------|
|                                    | VOLUVEN<br>N=49 | Hetastarch<br>N=51 | Estimate                 | 95% CI         |
| Calculated red blood cell loss [L] | 1.17            | 1.31               | 0.910                    | [0.720; 1.141] |
| Factor VIII [%]*                   | 100.5           | 81.4               | 1.244                    | [1.000; 1.563] |
| von Willebrand factor [%]*         | 97.7            | 88.7               | 1.128                    | [0.991; 1.285] |
| Fresh frozen plasma [mL]*          | 72              | 144                | 0.723                    | [0.000; 2.437] |

\*Exploratory analyses

There was no statistically significant difference between the two treatment groups with respect to the secondary efficacy endpoints of hemodynamic stability, body temperature,

hemodynamic parameters, blood pressure, central venous pressure, heart rate, fibrinogen and platelet count.

In addition to the US trial, three non-US trials were conducted with the primary objective of showing equivalency (based on mean difference rather than mean ratio as in the US study) between Voluven® and pentastarch in maintaining or restoring hemodynamic parameters. The largest of the three trials (N=100) met the prespecified boundary (-500 mL, 500 mL), but the two smaller studies (N=52 and N=59) did not.

In exploratory analyses, the effect of Voluven® on coagulation parameters (von Willebrand factor, Factor VIII, and Ristocetin cofactor) was shown to be significantly lower than pentastarch at one or more time points (US and non-US trials). These findings are consistent with the lower molar substitution, lower average molecular weight and narrower molecular weight distribution of Voluven® as compared to pentastarch resulting in a lower *in vivo* molecular weight and increased elimination from the circulation.

A safety profile of Voluven® at least as favorable as for pentastarch was also demonstrated in studies where Voluven® was administered at doses higher (up to 50 mL/kg or 3 g/kg) than for pentastarch (up to 33 mL/kg or 2 g/kg) in clinical settings where large or repetitive doses are administered. [see *Adverse Reactions* (6)]

## 15 REFERENCES

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- 2) Kozek-Langenecker S. Effects of hydroxyethyl starch solutions on hemostasis. *Anesthesiology* 2005; 103 (3): 654-60
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- 4) Jungheinrich C, Neff T. Pharmacokinetics of hydroxyethyl starch. *Clin Pharmacokinetik* 2005; 44 (7): 681-699
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- 6) Leuschner J, Opitz J, Winkler A, Scharpf R, Bepperling F. Tissue storage of <sup>14</sup>C-labeled hydroxyethyl starch (HES) 130/0.4 and HES 200/0.5 after repeated intravenous administration to rats. *Drugs R D* 2003; 4 (6): 331-8

7) Gandhi SD, Weiskopf RB, Jungheinrich C et al. Volume replacement therapy during major orthopedic surgery using Voluven<sup>®</sup> (hydroxyethyl starch 130/0.4) or hetastarch. Anesthesiology 2007; 106:1120-1127

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Voluven<sup>®</sup> (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) for intravenous infusion is supplied in the following primary container and carton sizes:

Polyolefin bag (**freeflex**<sup>®</sup>) with overwrap: 500 mL  
Carton of 15 x 500 mL  
NDC 0409-1029-01

Store at 15° to 25°C (59° to 77°F). Do not freeze.

## 17 PATIENT COUNSELING INFORMATION

Because this product is not used directly by patients, patient counseling or instructions for use by patients is not considered necessary.

Manufactured by: Fresenius Kabi Norge AS,  
P.O. Box 430,  
NO-1753 HALDEN, NORWAY

Distributed by:  
Hospira, Inc.  
275 North Field Drive  
Lake Forest, Illinois 60045 USA

Made in Norway

EN-1597



## Product Approval Information - New Drug Applications

December 27, 2007

Our reference: NDA BN070012

Fresenius Kabi  
Attention: W. Gerald Cohn  
c/o Carolina Research Group, Inc.  
P.O. Box 32295  
Raleigh, NC 27622

Dear Mr. Cohn:

Please refer to your new drug application dated February 28, 2007 and received March 1, 2007, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for 6% Hydroxyethyl Starch in 0.9% Sodium Chloride Infusion (Voluven® 500 mL freeflex® flexible plastic intravenous solution container).

We acknowledge receipt of your submissions dated February 28; March 30; June 25 and 26; July 26; August 16 and 17; September 6 and 20; October 2, 4, 12, and 17; November 9, 14, 16, 27, and 30; and December 3 and 10, 2007

This new drug application provides for the use of 6% Hydroxyethyl Starch in 0.9% Sodium Chloride Infusion ((Voluven® 500 mL **freeflex**® flexible plastic intravenous solution container) for treatment and prophylaxis of hypovolemia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA BN070012.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

We remind you of your postmarketing study commitments in your submission dated November 30, 2007. The commitments are listed below.

1. To perform a multiple-dose randomized controlled trial (RCT) to be conducted in

subjects with severe sepsis including subjects with renal dysfunction and at risk for deterioration of renal dysfunction. Fresenius Kabi will submit the final Clinical Study Protocol of this Phase 3b study entitled "Crystalloids or colloids in patients with severe sepsis: effects on hemodynamics and tolerability of enteral nutrition" (Short title: CRYSTMAS, study code 06-HE06-01) within 3 months of the Approval Letter and will submit the final Clinical Study Report to FDA within 36 months of the Approval Letter.

Protocol Submission: by within 3 months of the date of this letter

Final Report Submission: by within 36 months of the date of this letter

2. Fresenius Kabi commits to perform a randomized controlled trial (RCT) to be conducted in children in the age group of 2 to 12 years. Fresenius Kabi will submit the final Clinical Study Protocol of this Phase 3 study entitled "Efficacy and safety of 6 % hydroxyethyl starch 130/0.4 ((Voluven®) vs 5% HSA in volume substitution therapy during open-heart surgery in 2 to 12 years old pediatric patients" within 12 months of the Approval Letter and will submit the final Clinical Study Report to FDA within 36 months of the Approval Letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Blood Applications and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Advertising and Promotional Labeling Branch (HFM-602)  
1401 Rockville Pike, Suite 200 North  
Rockville, MD 20852-1448

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm).

FDA has determined that referral of this application to the Blood Products Advisory Committee (BPAC) prior to approval (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]) was not needed for the following reasons: Voluven®'s mechanism of action as a plasma volume expander indicated for the treatment and prophylaxis of hypovolemia is well studied and understood. The European-approved Voluven® product manufactured by Fresenius Kabi has demonstrated comparable safety and efficacy with similar products, such as hetastarch and pentastarch. Studies to evaluate the efficacy of Voluven® were adequate and the results did not raise any concerns related to safety. Review of information submitted in the NDA for Voluven® did not raise any controversial issues or pose unanswered scientific questions which would have benefited from advisory committee discussion and recommendations.

If you have any questions, please contact Franklin T. Stephenson, Regulatory Project Manager, at (301) 827-6165.

Sincerely,

/signed/

Jay S Epstein, M.D.  
Director Office of Blood Research and Review  
Center for Biologics  
Evaluation and Research

Enclosure: Package Insert (PDF, 233 KB)

Updated: December 27, 2007



US005218108A

**United States Patent** [19]  
Sommermeyer et al.

[11] **Patent Number:** 5,218,108  
[45] **Date of Patent:** Jun. 8, 1993

[54] **HYDROXYLETHYLSTARCH (HES) AS  
PLASMA EXPANDER AND PROCESS FOR  
PREPARING HES**

[75] **Inventors:** Klaus Sommermeyer; Franz Cech;  
Burghard Weidler; all of Rosbach;  
Klaus Henning, Usingen, all of Fed.  
Rep. of Germany

[73] **Assignee:** Fresenius AG, Bad Homburg, Fed.  
Rep. of Germany

[21] **Appl. No.:** 533,294

[22] **Filed:** Jun. 5, 1990

[30] **Foreign Application Priority Data**

Jun. 16, 1989 [DE] Fed. Rep. of Germany ..... 3919729

[51] **Int. Cl.<sup>5</sup>** ..... C08B 31/10; A61K 31/72

[52] **U.S. Cl.** ..... 536/111; 514/60

[58] **Field of Search** ..... 536/111; 514/60

[56] **References Cited**

**U.S. PATENT DOCUMENTS**

4,474,951 10/1984 Pope ..... 536/111  
4,629,698 12/1986 Nitsch et al. .... 435/98  
4,716,186 12/1987 Portnoy et al. .... 536/111  
4,837,314 6/1989 Eastman ..... 536/111

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935339 8/1963 United Kingdom .

*Primary Examiner*—Nathan M. Nutter  
*Attorney, Agent, or Firm*—Omri M. Behr; Matthew J.  
McDonald

[57] **ABSTRACT**

A hydroxyethyl starch for use as plasma expander which is obtainable by hydrolytic predegradation of a starch rich in amylopectin, partial hydroxyethylation to a specific substitution degree in the presence of alkali and subsequent hydrolytic degradation to a specific molecular weight, comprises a mean molecular weight of 60,000–600,000 and a substitution degree MS of 0.15–0.5. The ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8–20 and the substitution degree DS lies in the range from 0.15 to 0.5. A process for the preparation of this hydroxyethyl starch employs 2-chloroethanol as hydroxyethylation agent. The hydroxyethylation is carried out under alkaline conditions at room temperature, the pH value held at a value of about 12 and the temperature held at a value of about 20° C.

**7 Claims, No Drawings**

# HYDROXYETHYLSTARCH (HES) AS PLASMA EXPANDER AND PROCESS FOR PREPARING HES

The field of volume substitution (e.g. hemorrhagic shock) or hemodilution (e.g. arterial occlusive disease, Fontaine II B, III) is today inconceivable without the use of colloidal plasma substitutes. For both these indications, of the exogeneous plasma substitutes (starch, gelatins, dextran), hydroxyethyl starch (HES) has found the greatest acceptance in recent years.

The lower disturbance of coagulation and the clearly reduced incidence of serious anaphylactoid reactions compared with dextran are responsible for the good acceptance of hydroxyethyl starch in the field of volume replacement and hemodilution. In addition, it has been possible to show that the volume efficacy of hydroxyethyl starch, depending on the indication, may be referred to as sufficient to good, a differentiated therapy being possible, depending on the state of the patient, by using the various known hydroxyethyl starch preparations differing in molecular weight and substitution degree. The factor considered particularly favourable here is the low colloid osmotic pressure of starch solutions compared with dextrans. With regard to the kidneys, the lower urine viscosity involves a lesser risk of a decrease in functional activity. In the area of hemodilution, in addition to the reduction of hematocrit, the reduction of plasma viscosity in particular has proved to be a therapeutically effective principle of HES-induced rheological improvement. Therapeutical advantages are obtained over other exogeneous plasma substitutes.

Already known hydroxyethyl starches used as plasma expanders have different molecular weights  $M_w$  and substitution degrees MS and DS as well as different substitution patterns.

Due to the use of the natural starting raw material amylopectin and the production process in which to a certain extent a cleaving of the polymer chains is necessary, the hydroxyethyl starch is not present as molecular unitary substance with defined molecular weight but as mixture of molecules of different size which are also differently substituted by hydroxyethyl groups. The characterization of such mixtures requires the aid of statistically determined magnitudes (cf. K. Sommermeyer et al., "Clinically employed hydroxyethyl starch: physical chemical characterization", *Krankenhauspharmazie*, 271 (1987)). To denote the average molecular weight, the mean molecular weight  $M_w$  is used. The general definition of this mean value is:

$$M_w = \frac{\sum_i N_i \cdot M_i^2}{\sum_i N_i \cdot M_i}$$

There are two differently defined substitution degrees for defining the substitution by hydroxyethyl groups.

The substitution degree MS (molar substitution) is defined as the average number of hydroxyethyl groups per anhydroglucose unit. It is determined from the total number of hydroxyethyl groups in a specimen, for example in accordance with Morgan, by ether splitting and subsequent quantitative determination of ethyl iodide and ethylene, which are thereby formed.

In contrast, the substitution degree DS (degree of substitution) is defined as the proportion of the substi-

tuted anhydroglucose units of all anhydroglucose units. It can be determined from the measured amount of the unsubstituted glucose after hydrolysis of a specimen. It follows from these definitions that  $MS > DS$ . In the case where only monosubstitution is present, i.e. each substituted anhydroglucose unit carries only one hydroxyethyl group,  $MS = DS$ .

It is known that  $\alpha$ -amylase breaks down hydroxyethyl starches in the sense that only glycosidic bonds of unsubstituted anhydroglucose units are split. It is further known that with increasing degree of substitution MS or DS the elimination of hydroxyethyl starches from the plasma is retarded.

It is moreover known that for the same MS, DS and the same molecular weight distribution starches substituted mainly in the 6-position are eliminated faster than starches substituted mainly in the 2-position.

In this respect, only hydroxyethyl starches having a low C2/C6 ratio or being highly substituted were used for pharmaceutical purposes.

Thus, GB-PS 1,395,777 describes hydroxyethyl starches substituted predominantly in 6-position corresponding to a C2/C6 ratio of 0.5 to 2.0. These hydroxyethyl starches are made by reaction of wax maize starch with ethylene oxide with alkali in excess.

DE-OS 2,814,032 describes a process for preparing hydroxyl starch suitable as blood plasma expander, the starch being alkaline hydroxyethylated, the reaction mixture then neutralized and the hydroxyethyl starch formed extracted from the reaction mixture with a solvent, such as dimethyl formamide in which the salts formed by the neutralization are only sparingly soluble or not soluble at all. The hydroxyethyl starch obtained has a molar ratio of 2-O-hydroxyethyl anhydroglucose to 6-O-hydroxyethyl anhydroglucose of about 1.

According to the process described in DE-OS 3,313,600 for preparing plasma expanders on a starch basis in which the degradation step of the starch rich in amylopectin is at least partially carried out enzymatically, the breaking down of the starch is performed to a molecular weight of 40,000 to 1,000,000 Dalton, in particular from 200,000 to 450,000 Dalton, and the etherification to a substitution degree (MS) of 0.1 to 0.8 or 0.5 to 0.8, in particular 0.5 to 0.7 (cf. page 8, paragraph 3). The ratio of the substitution of C2 compared with the substitution of C6 is low (cf. page 5, paragraph 2).

The aforementioned hydroxyethyl starches have the disadvantage that they do not ensure a complete degradability from the plasma within a period of about 6-12 hours and moreover, due to their high substitution degree MS ( $MS > 0.5$ ), involve the danger that with the usual repetition infusions over longer periods of time an accumulation of difficultly eliminatable components takes place in the serum and tissue. Due to this long-time storing, allergic reactions may occur, for example nettle rash, etc.

The problem underlying the invention is therefore to make available a hydroxyethyl starch which can be completely broken down within a physiologically reasonable time.

A further problem resides in making available an HES which nevertheless due to the choice of a suitable MS or DS value and the molecular weight has a controllable elimination behaviour.

The starting products for recovering hydroxyethyl starch are starches having a high content of amylopectin, the highly branched component of starch, in partic-

ular potato starch, wax maize starch, sorghum starch or waxy rice starch.

For a coarse presetting of the intended molecular weight these starches are subjected to a hydrolytic degradation reaction. The molecular weight is reduced here from about 20,000,000 Dalton to several million Dalton.

In the subsequent alkaline hydroxyethylation with known hydroxyethylation agents, it is possible to introduce a hydroxyethyl group into position 2, 3 and 6 of the anhydroglucose unit. Disubstituted units, such as 2,3-dihydroxyethyl anhydroglucose, 2,6-dihydroxyethyl anhydroglucose are formed in the synthesis with less probability. The reactivity of the individual hydroxy groups in the unsubstituted anhydroglucose unit compared with hydroxyethylation is different depending on the reaction conditions. Within certain limits, the substitution pattern, i.e. the individual differently substituted anhydroglucoses statistically shared amongst the individual polymer molecules, can thereby be influenced. Advantageously, predominantly the 2 and the 6-position is hydroxyethylated, the 6-position being preferred due to easier accessibility.

The objective of the present invention, that is the preparation of a hydroxyethyl starch which can be completely broken down within a physiologically reasonable period and which on the other hand nevertheless has a controllable elimination behaviour, is achieved by a starch substituted predominantly in 2-position and substituted as homogeneously as possible, MS being approximately equal to DS.

The predominant 2-substitution makes the hydroxyethyl starch relatively difficult to degrade for  $\alpha$ -amylase. It is advantageous to avoid as far as possible the occurrence of substituted anhydroglucose units one behind the other within the polymer molecule in order to guarantee complete degradability.

This can be achieved in that the substitution is accordingly low, enabling the molecules to derivate statistically in the sense of a substitution distributed over the total molecules. This results in substituted anhydroglucoses at a relatively large distance apart, compensating the effect of the retardation of the  $\alpha$ -amylase degradation due to the predominant 2-substitution and enabling a controllability of the degradation rate to be achieved.

It has been found that hydroxyethyl starches substituted extremely low ( $MS < 0.5$ ) and having a high ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units are rapidly and completely eliminated from the human body within the first hours of the infusion.

It has further been found that such hydroxyethyl starches, in spite of the low substitution, contrary to the opinion of those skilled in the art, do have an adequately high solubility in aqueous medium so that the solutions are stable even for relatively long periods of time and do not form any agglomerates or gels which would make the further use as plasma expander solution impossible.

Hydroxyethyl starches with the characteristics described above therefore combine the general advantages of hydroxyethyl starch compared with other plasma expander types, such as gelatins or dextran, and avoids the disadvantages of the hitherto known hydroxyethyl starch types used for the indications described.

Hydroxyethyl starches having the aforementioned properties can be obtained with the aid of a process including essentially the following steps:

a) Preextraction of the starch used with methanol to remove vegetable dyes and to block reactive groups. Thus, for example, reactive aldehyde groups are partially inactivated by acetal formation.

b) Methanolic hydrolysis for coarse setting of the molecular weight with a 20-40%, preferably 30% methanolic suspension of the starch with 1% HCl, the latter being held for 2-4 h, preferably 3 h, at 30°-50° C., preferably 40° C. The end of the reaction is achieved by neutralization with 1 NaOH and subsequent cooling to room temperature. Thereafter the suspension is washed free of chloride.

c) Alkali wash for protein extraction, a 30-50%, preferably 40% suspension in 0.1 N NaOH being prepared and this being held 1-3 h, preferably 2 h, at 30°-50° C., preferably 40° C. Thereafter the procedure is repeated at room temperature.

d) Hydroxyethylation with a hydroxyethylating agent, for example ethylene oxide, and in a particularly preferred embodiment, 2-chloroethanol, the molar ratio of pretreated starch to hydroxyethylating agent being adapted to the desired substitution degree. The starch is dissolved under nitrogen in 20-40%, preferably 30% suspension, in 1 N NaOH for 2 h at 30°-50° C., preferably 40° C. Within 6-10 hrs., preferably 7-8 hrs., the hydroxyethylating agent is added in drops at room temperature, the addition of 10 N NaOH preventing the pH value dropping below 12. Thereafter, this is neutralized with 10% HCl.

e) The solution is heated to 40°-70° C., preferably 60° C., mixed with 0.2% HCl and the hydrolysis followed viscosimetrically. The reaction is terminated by neutralization with NaOH and cooling to room temperature.

f) Purification by filtration through a depth filter and ultrafiltration through a hollow fibre module with a separating limit of about 30,000 Dalton.

g) Spray drying of the end products in a manner known per se.

The hydroxyethyl starches according to the invention are also suitable as carbohydrate components in enteral nutrition of diabetics because the same considerations apply as regards the degradability.

The invention will be explained in detail hereinafter with the aid of an example.

500 g wax maize starch is suspended in a litre of dry methanol and brought to boil. After cooling the methanol is sucked off and the starch washed with water. The washing operation is repeated once.

The starch with a residual moisture content of 28.13% is hydrolyzed in 30% methanolic suspension with 1% HCl for three hours at 40° C. The reaction is stopped by neutralization with 1 N NaOH in methanol and cooling to room temperature. After extraction the starch exhibits a residual moisture content of 16.12% and a mean molecular weight of 900,000.

The starch is suspended in a litre H<sub>2</sub>O, extracted and washed free of chloride. After suction drying the starch has a residual moisture content of 51.29%.

The starch is thereafter stirred in 40% suspension in 0.1 N NaOH for 2 hours at 40° C., again cooled to room temperature and dried by exhaustion (residual moisture content 48.60%). The operation is repeated once at room temperature.

418.0 g (2.58 Mol) of pretreated starch are dissolved in 30% suspension in 1 N NaOH at 40° C. under nitro-

gen. Within 7-8 hrs., 51.9 ml (0.77 Mol) 2-chloroethanol is dripped in. By adding NaOH reduction of the pH value below 12 is avoided. Thereafter, neutralization is carried out with 10% HCl.

The solution is filtered after 1:1 dilution with water via a depth filter (Seitz T750).

The solution is thereafter heated to 60° C., set with 25% HCl to an HCl concentration of 0.2 and hydrolyzed for 4 hours.

The solution is neutralized by addition of sodium hydroxide to pH 6.0 and cooled to room temperature. Thereafter, filtration is carried out via a Seitz EKS filter.

The clear solution is now ultrafiltrated via a hollow fibre module with a separation limit of about 30,000 Dalton and the remaining retentate spray dried.

A hydroxyethyl starch is obtained having a mean molecular weight of 234,000 and a molar substitution degree of 0.26. The C2/C6 ratio is 9.34. The hydroxyethyl starch prepared in this manner has the following substitution pattern (area percentages) which can be determined by complete hydrolysis of HES and subsequent determination of glucose and its hydroxyethyl derivatives via trimethyl silylation:

|                               |        |
|-------------------------------|--------|
| glucose:                      | 81.42% |
| 2-O-hydroxyethyl glucose:     | 12.42% |
| 3-O-hydroxyethyl glucose:     | 2.70%  |
| 6-O-hydroxyethyl glucose:     | 1.33%  |
| 2,2-O-dihydroxyethyl glucose: | 0.21%  |
| 2,3-O-dihydroxyethyl glucose: | 0.51%  |
| 2,6-O-dihydroxyethyl glucose: | 0.17%  |
| 3,3-O-dihydroxyethyl glucose: | 0.10%  |
| 3,6-O-dihydroxyethyl glucose: | 0.05%  |

We claim:

1. Hydroxyethyl starch for use as plasma expander obtainable by hydrolytic pre-degradation of a starch rich in amylopectin, partial hydroxyethylation up to a certain substitution degree in the presence of alkali and subsequent hydrolytic degradation to a certain molecular weight, characterized in that it has a mean molecular weight of 60,000-600,000 and a substitution degree MS of 0.15 to 0.5, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and

the substitution degree DS lies in the range from 0.15 to 0.5.

2. Hydroxyethyl starch according to claim 1, characterized in that it has a mean molecular weight of 80,000 to 400,000 and a substitution degree MS of 0.2-0.4, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.15 to 0.40.

3. Hydroxyethyl starch according to claim 1, characterized in that it has a mean molecular weight of 100,000 to 300,000 and a substitution degree MS of 0.25-0.35, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.2 to 0.35.

4. A hydroxyethyl starch for use as plasma expander characterized in that

it has a mean molecular weight of 60,000-600,000 and a substitution degree MS of 0.15 to 0.5,

the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.15 to 0.5, produced by a process wherein:

- a) starch having a content of amylopectin of >95% is pre-extracted with methanol,
  - b) the starch is brought by acid hydrolysis to a suitable mean molecular weight,
  - c) the starch is subjected to an alkali wash,
  - d) the starch is hydroxyethylated by means of a hydroxyethylation agent under alkaline conditions,
  - e) the molecular weight is exactly set by acid hydrolysis,
  - f) the hydroxyethyl starch thus obtained is pulled, and
  - g) spray dried,
- characterized in that the hydroxyethylation agent used is selected from the group consisting of 2-chloroethanol and ethylene oxide and the hydroxyethylation is carried out under alkaline conditions at room temperature.

5. A starch of claim 4 characterized in that the pH value is kept at a value of about 12 during the hydroxyethylation.

6. A starch of claim 4 characterized in that the temperature is kept at a value of about 20° to 25° C.

7. A starch of claim 4 characterized in that the hydroxyethyl starch is purified by filtration and ultrafiltration.

\* \* \* \* \*



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DATE PRINTED  
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OMRI M. BEHR, ESQ.  
325 PIERSON AVENUE  
EDISON NJ 08837

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|------------------|------------|---------------|--------------|-------------------------------|-------------------------|-------------------------|-----------------|------------------|--------------------|
| 5,218,108        | \$3,320.00 | \$0.00        | 11/24/04     | 07/533,294                    | 06/08/93                | 06/05/90                | 12              | NO               | LUDR3.0-036        |



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|------------------|------------|---------------|--------------|-------------------------------|-------------------------|-------------------------|-----------------|------------------|--------------------|
| 5,218,108        | \$1,950.00 | \$0.00        | 11/13/00     | 07/533,294                    | 06/08/93                | 06/05/90                | 08              | NO               | LUDR3.0-036        |



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EDISON NJ 08837

## MAINTENANCE FEE STATEMENT

According to the records of the U.S. Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450.

| PATENT<br>NUMBER | FEE AMT    | SUR<br>CHARGE | PYMT<br>DATE | U.S.<br>APPLICATION<br>NUMBER | PATENT<br>ISSUE<br>DATE | APPL.<br>FILING<br>DATE | PAYMENT<br>YEAR | SMALL<br>ENTITY? | ATTY DKT<br>NUMBER |
|------------------|------------|---------------|--------------|-------------------------------|-------------------------|-------------------------|-----------------|------------------|--------------------|
| 5,218,108        | \$1,020.00 | \$0.00        | 11/25/96     | 07/533,294                    | 06/08/93                | 06/05/90                | 04              | NO               | LUDR3.0-036        |



Fresenius  
Kabi

### **Voluven 6 % Solution for Infusion**

Listing of the actual registrations within EU and Non-EU countries

| <b>Country</b>                    | <b>Reg-Date</b> | <b>Reg-No.</b> |
|-----------------------------------|-----------------|----------------|
| Germany<br>(Voluven)              | 22-Jun-1999     | 42093.00.00    |
| Germany<br>(Voluven<br>Fresenius) | 26-Aug-1999     | 45010.00.00    |
| Germany<br>(Voluven 6%)           | 26-Aug-1999     | 44943.00.00    |

Registrations based on the German marketing authorisation no. 42093.00.00

| <b>Country</b> | <b>Reg-Date</b> | <b>Reg-No.</b> |
|----------------|-----------------|----------------|
| Switzerland    | 27-Jun-2000     | 55093          |



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Food and Drug Administration  
1401 Rockville Pike  
Rockville MD 20852-1448

Our Reference: BB-IND 9740

April 5, 2001

Fresenius Kabi Deutschland, GmbH  
Attention: Rosemary P. Davis  
Manager Of Regulatory Affairs  
P.O. Box 597  
8484 US 70 West  
Clayton, NC 27520-0597



Dear Ms. Davis:

The Center for Biologics Evaluation and Research has received your **Investigational New Drug Application (IND)**. The following product name and BB-IND number have been assigned to this application. They serve only to identify it and do not imply that this Center either endorses or does not endorse your application.

BB-IND #: 9740

SPONSOR: **Fresenius Kabi Deutschland, GmbH**

PRODUCT NAME: **High Molecular Weight Hydroxyethyl Starch - 6% (Voluven)**

DATE OF SUBMISSION: **March 23, 2001**

DATE OF RECEIPT: **March 26, 2001**

This BB-IND number should be used to identify all future correspondence and submissions, as well as telephone inquiries concerning this IND. Please provide an **original and two copies of every submission to this file**. Please include three originals of all illustrations which do not reproduce well.

It is understood that studies in humans will not be initiated until 30 days after the date of receipt shown above. If this office notifies you, verbally or in writing, of serious deficiencies that require correction before human studies can begin, it is understood that you will continue to withhold such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory. If such a clinical hold is placed on this file, you will be notified in writing of the reasons for placing the IND on hold.

You are responsible for compliance with applicable portions of the Public Health Service Act, the Federal Food, Drug, and Cosmetic Act, and the Code of Federal Regulations (CFR). A copy of 21 CFR Part 312, pertaining to INDs, is enclosed. Copies of other pertinent regulations are

Page 2 - BB-IND 9740

available from this Center upon request. The following points regarding obligations of an IND sponsor are included for your information only, and are not intended to be comprehensive.

Progress reports are required at intervals not exceeding one year and are due within 60 days of the anniversary of the date that the IND went into effect. Any unexpected, fatal or immediately life-threatening reaction which is associated with use of this product must be reported to this Center within three working days, and all serious, unexpected adverse experiences must be reported, in writing, to this Center and to all study centers within ten working days.

Charging for an investigational product in a clinical trial under an IND is not permitted without the prior written approval of the FDA.

Prior to use of each new lot of the investigational biologic in clinical trials, please submit the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results).

If not included in your submission, please provide copies of the consent forms for each clinical study. A copy of the requirements for and elements of informed consent are enclosed. Also, please provide documentation of the institutional review board approval(s) for each clinical study.

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR Part 58, copies available upon request). If such studies have not been conducted in compliance with these regulations, please provide a statement describing in detail all differences between the practices used and those required in the regulations.

Item 7a of form FDA 1571 requests that either an "environmental assessment," or a "claim for categorical exclusion" from the requirements for environmental assessment, be included in the IND. If you did not include a response to this item with your application, please submit one. See the enclosed information sheet for additional information on how these requirements may be addressed.

Sponsors of INDs for products used to treat life-threatening or severely debilitating diseases are encouraged to consider the interim rule outlined in 21 CFR 312.80 through 312.88.

Telephone inquiries concerning this IND should be made directly to me at (301) 827-3524.

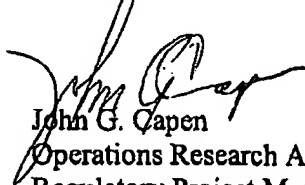
Correspondence regarding this file should be addressed as follows:

Center for Biologics Evaluation and Research  
ATTN: Office of Blood Research and Review  
HFM 99, Room 200N  
1401 Rockville Pike  
Rockville, MD 20852-1448

Page 3 - BB-IND 9740

If we have any comments after we have reviewed this submission, we will contact you.

Sincerely yours,



John G. Capen

Operations Research Analyst  
Regulatory Project Management Branch  
Division of Blood Applications  
Office of Blood Research and Review  
Center for Biologics Evaluation and Research

Enclosures (3):

21 CFR Part 312  
21 CFR 50.20, 50.25  
Information sheet on 21 CFR 25.24

***Regulatory Correspondence/Contacts Log***

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**2000**

**August 29, 2000**

**PRE-IND MEETING**

Clinical study design was discussed in detail and the FDA provided a number of specific recommendations on study design and size as well as on endpoints and other documentation to be captured in the study.

**2001**

**March 23, 2001**

**SUBMISSION OF IND (BB-IND 9740)**

**April 5, 2001**

**FDA ACKNOWLEDGES RECEIPT OF IND**

**May 30, 2001**

**RECEIPT OF FDA QUESTIONS AND REQUEST  
FOR PROTOCOL AMENDMENT**

**July 6, 2001**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 001)**

Response to FDA letter dated May 30, 2001

**September 2001**

**START OF PHASE III STUDY HS-13-30-US**

**August 2, 2001**

**SUBMISSION OF INFORMATION AMENDMENT  
(Serial No. 002)**

Submission of documentation for a compatibility study

***Regulatory Correspondence/Contacts Log***

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**2002**

**January 17, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 003)**

Submission of positive votes and final informed consent form for all centers

**May 8, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 004)**

Change in protocol

**June 25, 2002**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 005)**

**July 17, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 006)**

Protocol signature of 2 new principal investigators

**September 16, 2002**

**FDA LETTER RECEIVED**

Questions and comments on IND submission dated May 8, 2002  
(Serial No. 004) obtained

**October 7, 2002**

**SUBMISSION OF RESPONSE TO FDA LETTER  
DATED SEPTEMBER 16, 2002  
(Serial No. 007)**

**December 16, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 008)**

Closing of a study center etc.

**2003**

**May 8, 2003**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 009)**

***Regulatory Correspondence/Contacts Log***

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Inclusion of additional subinvestigator etc.

**July 1, 2003**

**SUBMISSION OF INFORMATION AMENDMENT  
(Serial No. 010)**

Submission of documentation for a compatibility study

**July 22, 2003**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 011)**

**2004**

**June 24, 2004**

**REQUEST FOR PRE-NDA TYPE B MEETING  
(Serial No. 012)**

**July 5, 2005**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 013)**

**July 28, 2004**

**REQUEST FOR PRE-NDA TYPE B MEETING  
(Serial No. 014)**

**September 1, 2004**

**PRE-NDA MEETING WITH FDA**

Requested Pre-NDA Type B Meeting held with FDA

**October 19, 2004**

**SUBMISSION OF GENERAL CORRESPONDENCE  
(Serial No. 015)**

Designation of domestic agent

**October 20, 2004**

**SUBMISSION OF GENERAL CORRESPONDENCE  
(Serial No. 016)**

Study termination in all centers

***Regulatory Correspondence/Contacts Log***

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**2005**

**June 29, 2005**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 017)**

**2006**

**February 9, 2006**

**SUBMISSION OF GENERAL CORRESPONDENCE  
(Serial No. 018)**

Submission of safety data base

**July 13, 2006**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 019)**

**2007**

**September 14, 2007**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 020)**

***Regulatory Correspondence/Contacts Log***

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**2007**

|                          |   |                            |
|--------------------------|---|----------------------------|
| <b>February 28, 2007</b> | <b>SUBMISSION</b>   | <b>ORIGINAL NDA</b>        |
|                          | Submission of original NDA  |                            |
| <b>March 23, 2007</b>    | <b>CORRESPONDENCE FROM FDA</b>  |                            |
|                          | FDA acknowledges receipt of NDA on March 1, 2007                        |                            |
| <b>March 30, 2007</b>    | <b>TELECON FROM FDA</b>   |                            |
|                          | FDA request additional copy of Module 3 and Methods Validation Package  |                            |
| <b>March 30, 2007</b>    | <b>SUBMISSION</b>   | <b>NDA COPIES</b>          |
|                          | Submission of requested copy of Module 3 and Methods Validation Package |                            |
| <b>April 30, 2007</b>    | <b>CORRESPONDENCE FROM FDA</b>  |                            |
|                          | FDA advises that NDA is filed.  |                            |
| <b>June 11, 2007</b>     | <b>TELECON FROM FDA</b>   |                            |
|                          | FDA requested teleconference.   |                            |
| <b>June 11, 2007</b>     | <b>FAX FROM FDA</b>   | <b>INFORMATION REQUEST</b> |
|                          | FDA sends fax to list questions of FDA reviewers.                       |                            |
| <b>June 12, 2007</b>     | <b>TELECONS TO/FROM FDA</b>   |                            |

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*Regulatory Correspondence/Contacts Log*

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|               |  |                         |
|---------------|--|-------------------------|
| June 13, 2007 | TELECON TO FDA   |                         |
| June 13, 2007 | EMAIL FROM FDA   |                         |
| June 13, 2007 | EMAIL TO FDA   |                         |
| June 18, 2007 | TELECONFERENCE WITH FDA  |                         |
| June 18, 2007 | EMAIL TO FDA   |                         |
| June 18, 2007 | EMAIL FROM FDA   |                         |
| June 25, 2007 | SUBMISSION   | NDA AMENDMENT           |
|               | Submission of response to FDA questions.                               |                         |
| June 26, 2007 | SUBMISSION   | SAFETY UPDATE<br>REPORT |
|               | Submission of first safety update report.<br>(Seven volume submission) |                         |
| June 28, 2007 | EMAIL TO FDA   |                         |
| June 29, 2007 | EMAIL FROM FDA   |                         |
| July 18, 2007 | FAX FROM FDA   | INFORMATION<br>REQUEST  |

**Regulatory Correspondence/Contacts Log**

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|                          |   |                            |
|--------------------------|---|----------------------------|
| <b>July 26, 2007</b>     | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>       |
|                          | Submission of response to FDA questions presented in fax of July 18.                      |                            |
| <b>July 30, 2007</b>     | <b>FAX FROM FDA</b>   | <b>INFORMATION REQUEST</b> |
|                          | FDA sends fax to request information on CMC and clinical matters.                         |                            |
| <b>August 6, 2007</b>    | <b>TELECON TO FDA</b>   | <b>INFORMATION REQUEST</b> |
| <b>August 16, 2007</b>   | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>       |
|                          | Submission of response to FDA questions presented in fax of July 30.                      |                            |
| <b>August 17, 2007</b>   | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>       |
|                          | Submission of draft Summary Basis of Approval as requested by FDA in telecon of August 6. |                            |
| <b>August 21, 2007</b>   | <b>TELECON TO FDA</b>   | <b>ADMINISTRATIVE</b>      |
| <b>August 21, 2007</b>   | <b>EMAIL TO FDA</b>   | <b>ADMINISTRATIVE</b>      |
| <b>August 22, 2007</b>   | <b>EMAIL TO FDA</b>   | <b>ADMINISTRATIVE</b>      |
| <b>September 4, 2007</b> | <b>FAX FROM FDA</b>   | <b>INFORMATION REQUEST</b> |

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**Regulatory Correspondence/Contacts Log**

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|-----------------------|--|--------------------------|
| September 6, 2007     | SUBMISSION   | NDA AMENDMENT            |
|                       | Submission of information in response to FDA fax of September 4, 2007.                             |                          |
| September 13, 2007    | FAX FROM FDA   | INFORMATION REQUEST      |
| September 19/20, 2007 | TELECONS FROM FDA  | INFORMATION REQUEST      |
| September 20, 2007    | SUBMISSION   | NDA AMENDMENT            |
|                       | Submission of information in response to FDA fax of September 13, 2007.                            |                          |
| September 20, 2007    | EMAIL FROM FDA   | INFORMATION REQUEST - PI |
| September 25, 2007    | TELECON TO FDA   | INFORMATION REQUEST      |
| October 1, 2007       | TELECON FROM FDA   | INFORMATION REQUEST      |
| October 2, 2007       | TELECON TO FDA   | INFORMATION REQUEST      |
| October 2, 2007       | SUBMISSION   | NDA AMENDMENT            |
|                       | Submission of information in response to FDA email of September 20, 2007 requesting PI revisions.. |                          |

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**Regulatory Correspondence/Contacts Log**

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|--------------------|--|-----------------------------|
| October 4, 2007    | SUBMISSION   | NDA AMENDMENT               |
|                    | Submission of information in response to FDA telecom of October 1, 2007 asking that request for approval of proprietary name be submitted. |                             |
| October 5, 2007    | TELECON/EMAIL<br>FROM FDA  | INFORMATION<br>REQUEST - PI |
| October 9/10, 2007 | TELECON TO FDA   | INFORMATION<br>REQUEST      |
| October 11, 2007   | EMAIL TO FDA   | INFORMATION<br>REQUEST      |
| October 12, 2007   | SUBMISSION   | NDA AMENDMENT               |
|                    | Submission of information in response to FDA email of October 5, 2007 requesting further PI revisions.                                     |                             |
| October 16, 2007   | TELECON FROM FDA   | TELECONFERENCE<br>REQUEST   |
| October 17, 2007   | TELECON TO FDA   | TELECONFERENCE<br>REQUEST   |
| October 17, 2007   | EMAIL TO FDA   | TELECONFERENCE<br>REQUEST   |
| October 17, 2007   | SUBMISSION   | NDA AMENDMENT               |
| October 18, 2007   | TELECON FROM FDA   | TELECONFERENCE<br>REQUEST   |
| October 22, 2007   | EMAIL TO FDA   | TELECONFERENCE<br>REQUEST   |

***Regulatory Correspondence/Contacts Log***

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|                  |                            |                           |
|------------------|----------------------------|---------------------------|
| October 23, 2007 | TELECON FROM FDA           | TELECONFERENCE<br>REQUEST |
| October 30, 2007 | EMAIL TO FDA               | TELECONFERENCE<br>REQUEST |
| October 31, 2007 | TELECONFERENCE<br>WITH FDA |                           |
| October 31, 2007 | TELECON FROM FDA           | ADMINISTRATIVE            |
| October 31, 2007 | EMAIL FROM FDA             | ADMINISTRATIVE            |
| November 2, 2007 | TELECON FROM FDA           | CLINICAL                  |
| November 6, 2007 | TELECON TO FDA             | CLINICAL                  |
| November 8, 2007 | TELECON TO FDA             | CLINICAL                  |
| November 8, 2007 | EMAIL TO FDA               | CLINICAL                  |
| November 9, 2007 | SUBMISSION                 | NDA AMENDMENT             |

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**Regulatory Correspondence/Contacts Log**

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|                   |                          |                             |
|-------------------|--------------------------|-----------------------------|
| November 9, 2007  | TELECONS FROM/<br>TO FDA | CLINICAL                    |
| November 9, 2007  | FAX TO FDA               | CLINICAL                    |
| November 9, 2007  | EMAIL/FAX<br>FROM FDA    | INFORMATION<br>REQUEST - PI |
| November 13, 2007 | EMAIL TO FDA             | CLINICAL                    |
| November 13, 2007 | TELECON TO FDA           | PI REVISIONS                |
| November 14, 2007 | SUBMISSION               | NDA AMENDMENT               |
| November 16, 2007 | SUBMISSION               | NDA AMENDMENT               |
| November 26, 2007 | SUBMISSION               | NDA AMENDMENT               |
| November 28, 2007 | TELECON FROM FDA         | PI REVISIONS                |
| November 28, 2007 | EMAIL TO FDA             | PI REVISIONS                |
| November 29, 2007 | EMAIL FROM FDA           | PI REVISIONS/<br>CLINICAL   |
| November 29, 2007 | TELECONS TO FDA          | PI REVISIONS/<br>CLINICAL   |

**Regulatory Correspondence/Contacts Log**

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|                             |  |   |
|-----------------------------|--|---|
| <b>November 29/30, 2007</b> | <b>EMAILS TO/FROM FDA</b>              | <b>PI REVISIONS/<br/>CLINICAL</b>   |
| <b>November 30, 2007</b>    | <b>TELECONS/EMAILS<br/>TO/FROM FDA</b> | <b>PEDIATRIC STUDIES</b>  |
| <b>December 3, 2007</b>     | <b>SUBMISSION</b>                      | <b>NDA AMENDMENT</b><br><br>Submission of additional pediatric information as requested by FDA on November 30, 2007.  |
| <b>December 4, 2007</b>     | <b>EMAIL TO FDA</b>                    | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 5, 2007</b>     | <b>TELECON FROM FDA</b>                | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 5, 2007</b>     | <b>EMAIL TO FDA</b>                    | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 5, 2007</b>     | <b>SUBMISSION</b>                      | <b>NDA AMENDMENT</b><br><br>Submission of amendment containing PI revisions and information on PM study/commitment as requested by FDA on November 28-30, 2007. |
| <b>December 7, 2007</b>     | <b>TELECONS TO/FROM<br/>FDA</b>        | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 10, 2007</b>    | <b>TELECONS TO FDA</b>                 | <b>PI REVISIONS<br/>PM STUDY</b>  |

**Regulatory Correspondence/Contacts Log**

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|                             |   |  |
|-----------------------------|---|--|
| <b>December 10, 2007</b>    | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>                   |
|                             | Submission of amendment containing PI revisions requested by FDA on December 7, 2007 and PM commitment.                 |  |
| <b>December 10, 2007</b>    | <b>CORRESPONDENCE<br/>FROM FDA</b>  | <b>PROPRIETARY NAME<br/>ACCEPTANCE</b> |
|                             | FDA forwards letter stating that proprietary name is acceptable. A fax copy of the letter is sent on December 11, 2007. |  |
| <b>December 11-12, 2007</b> | <b>EMAIL TO FDA</b>   | <b>PI REVISIONS<br/>PM STUDY</b>       |
| <b>December 12/13, 2007</b> | <b>TELECON/EMAIL<br/>FROM FDA</b>   | <b>PI REVISIONS<br/>PM STUDY</b>       |
| <b>December 14, 2007</b>    | <b>TELECON FROM FDA</b>   | <b>PEDIATRIC DATA</b>                  |
| <b>December 17, 2007</b>    | <b>EMAIL TO FDA</b>   | <b>PEDIATRIC DATA</b>                  |
| <b>December 17, 2007</b>    | <b>TELECONFERENCE<br/>WITH FDA</b>  | <b>PEDIATRIC DATA</b>                  |
| <b>December 18, 2007</b>    | <b>TELECON TO FDA</b>   | <b>PEDIATRIC DATA</b>                  |
| <b>December 18, 2007</b>    | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>                   |
|                             | Submission of amendment containing proposal for pediatric study, commitment wording and PI revisions.                   |  |
| <b>December 19, 2007</b>    | <b>TELECON TO FDA</b>   | <b>PEDIATRIC DATA</b>                  |

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*Regulatory Correspondence/Contacts Log*

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|                          |                                      |                       |
|--------------------------|--------------------------------------|-----------------------|
| <b>December 20, 2007</b> | <b>TELECON/EMAIL<br/>TO/FROM FDA</b> | <b>PEDIATRIC DATA</b> |
| <b>December 27, 2007</b> | <b>FAX/TELECON<br/>FROM FDA</b>      | <b>NDA APPROVAL</b>   |
| <b>December 27, 2007</b> | <b>CORRESPONDENCE<br/>FROM FDA</b>   | <b>NDA APPROVAL</b>   |

NDA approval letter (postmarked December 31, 2007; received January 2, 2008)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentees: Klaus Sommermeyer, Franz Cech, Burghard Weidler, and Klaus Henning  
Patent No: 5,218,108  
Issued: June 8, 1993  
For: HYDROXYLETHYLSTARCH (HES) AS PLASMA EXPANDER AND  
PROCESS FOR PREPARING HES

Date: 2/21/08

Express Mail Label No. EV214 912 970 US

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

MAIL STOP HATCH-WAXMAN PTE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

This is an application for extension of patent term under 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.770 and 1.775 for U.S. Patent 5,218,108 ("the '108 Patent").

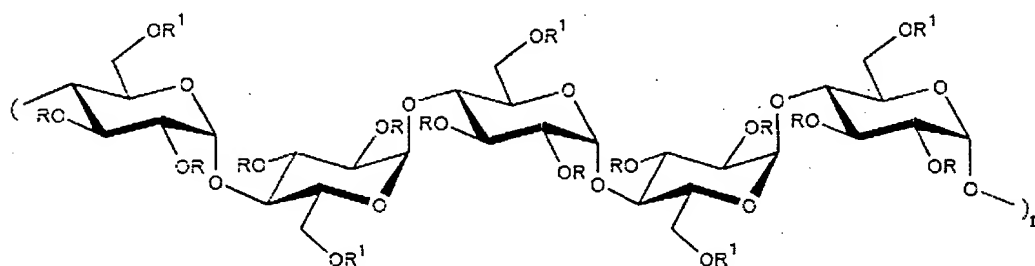
There is one owner of interest in the '108 Patent: Fresenius Kabi (referred to as the "Owner"). Copies of United States Patent and Trademark Office ("US PTO") records as well as additional documents confirming that title resides in the Owner is attached as Exhibit A.

Owner, through the undersigned, represent that it is the owners of record of the '108 Patent and hereby request an extension of the patent term.

The remainder of the sections of this application correspond with subparagraphs (1) to (15) of 37 C.F.R. § 1.740(a).

§1.740(a)(1): *A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.*

The following information is set forth in the package insert or product insert for the approved product. A copy of the Package Insert is included herein as Exhibit B. The brand name of the approved product is VOLUVEN®. The active ingredient of VOLUVEN® is 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection. Hydroxyethyl starch in VOLUVEN® is a synthetic colloid for use in plasma volume replacement. Hydroxyethyl starch is a derivative of thin boiling waxy corn starch, which mainly consists of a glucose polymer (amylopectin) predominately composed of  $\alpha$ -1-4-connected glucose units with several  $\alpha$ -1-6-branches. Substitution of hydroxyethyl groups on the glucose units of the polymer reduces the normal degradation of amylopectin by  $\alpha$ -amylase in the body. The chemical name of the class of hydroxyethyl starch is poly(O-2—hydroxyethyl) starch. The notation “130” in the active ingredient of VOLUVEN® indicates the mean molecular weight of the active ingredient, and specifically indicated that the mean molecular weight is 130,000 Daltons, with a range of 110,000 - 150,000 Daltons. The notation “0.4” indicates a low molar substitution by hydroxyethyl groups of 0.4 (with a range from 0.38 - 0.45) on glucose units of the starch. The low molar substitution (0.4) is the main pharmacological determinant for the beneficial effects of Voluven® on pharmacokinetics, intravascular volume and hemodilution. The pattern of hydroxyethyl substitution ( $C_2/C_6$  ratio) is approximately 9:1. The concentration is 6%. The structural formula of hydroxyethyl starch is, as depicted on the package insert, as follows:



R = -H, -CH<sub>2</sub>CH<sub>2</sub>OH  
 R¹ = -H, -CH<sub>2</sub>CH<sub>2</sub>OH or glucose units

§1.740(a)(2): *A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.*

Regulatory review occurred under Section 505(i) and 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (Title 21, United States Code Sections 355(i) and 355(b)(2)).

§1.740(a)(3): *An identification of date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.*

VOLUVEN® received approval in a letter dated December 27, 2007. A copy of the approval letter is attached as Exhibit C.

§1.740(a)(4): *In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.*

The sole active ingredient in VOLUVEN® is, as stated above, 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection. No product has been previously approved for commercial marketing or use under the Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act containing this active ingredient alone or in combination. This active ingredient differs from the active ingredients of other hydroxyethyl starch compositions currently available. For example, it is noted that a product Hextend®, containing a high molecular weight hetastarch having high molar substitution, was approved under NDA 20-0952 on March 31, 1999. According to the package insert for Hextend®, the hetastarch component of Hextend® is the same as in the approved Hetastarch Injection products (6% Hetastarch in 0.9% Sodium Chloride Injection). The mean molecular weight of the hetastarch of Hextend® is 670,000 Daltons with a range of 450,000 Daltons to 800,000 Daltons, and the molar substitution of the hetastarch of Hextend® is 0.75. The hydroxyethyl starch of Hextend® thus is

6% hydroxyethyl starch 670/0.75. Because the molecular weights differ so significantly and the molar substitutions also differ, and because of other factors such as branching, the active ingredient of VOLUVEN® differs from the active ingredient of the Hextend® product.

§1.740(a)(5): *A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.740(f) and an identification of the date of the last day on which the application could be submitted.*

This application is being submitted within the sixty day period following the approval of the VOLUVEN® NDA on December 27, 2007. We believe that the last day on which this submission can be made is February 25, 2008.

§1.740(a)(6): *A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.*

U.S. Patent 5,218,108

Inventors: Klaus Sommermeyer, Franz Cech, Burghard Weidler, and Klaus Henning

Issued: June 8, 1993

Filed: June 5, 1990

Date of Expiration: June 8, 2010

§1.740(a)(7): *A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.*

A copy of U.S. Patent 5,218,108, including the entire specification, claims, and drawings, is attached as Exhibit D.

§1.740(a)(8): *A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.*

No disclaimer or reexamination certificate has been issued for the '108 Patent. The first maintenance fee was paid on November 25, 1996; the second maintenance fee was paid on

November 13, 2000, and the third maintenance fee was paid on November 24, 2004. A copy of the USPTO maintenance fee record for this patent is attached as Exhibit E.

§1.740(a)(9): *A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product, if the listed claims include any claim to the approved product; (ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and (iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.*

Claims 1-7 of the '108 Patent are directed to pharmaceutical compositions comprising hydroxyethyl starch. The following chart shows how applicable patent Claims 1 and 2 read on Fresenius' approved product:

| <u>Claim</u>   | <u>Product</u>   |
|--|--|
| 1. Hydroxyethyl starch for use as plasma expander obtainable by hydrolytic pre-degradation of a starch rich in amylopectin, partial hydroxyethylation up to a certain substitution degree in the presence of alkali and subsequent hydrolytic degradation to a certain molecular weight, characterized in that | The approved product contains hydroxyethyl starch for use as a plasma expander, prepared by pre-degrading starch rich in amylopectin, followed by etherification which results in partial hydroxyethylation, and by subsequent hydrolytic degradation. |
| it has a mean molecular weight of 60,000-600,000 and a substitution degree MS of 0.15 to 0.5,  | The approved product has a mean molecular weight within this range, and a substitution degree MS within this range.  |
| the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and  | The approved product has such a ratio within this range.   |
| the substitution degree DS lies in the range from 0.15 to 0.5.   | The approved product has a substitution degree DS within this range.   |

|  |  |
|--|--|
| <p>2. Hydroxyethyl starch according to claim 1, characterized in that it has a mean molecular weight of 80,000 to 400,000 and a substitution degree MS of 0.2-0.4, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.15 to 0.40.</p> | <p>The approved product has these characteristics.</p> |
|--|--|

§1.740(a)(10): *A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:*

*(i) For a patent claiming a human drug, antibiotic, or human biological product:*

*(A) The effective date of the investigational new drug (IND) application and the IND number;*

*(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and*

*(C) The date on which the NDA was approved or the Product License issued.*

- (A) Fresenius Kabi filed an Investigational New Drug (IND) application, BB-IND 9740, ) for hydroxyethyl starch on March 23, 2001, and the FDA indicated that it was received on March 26, 2001, in a letter dated April 5, 2001. A copy of this letter is attached as Exhibit F. The IND has an effective date 30 days after the receipt of the IND, which is April 24, 2001.
- (B) Fresenius Kabi submitted a New Drug Application (NDA) on February 28, 2007, under BN070012.
- (C) The NDA was approved on December 27, 2007, under the existing NDA BN070012 to Fresenius Kabi (Exhibit C).

§1.740(a)(11): *A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.*

Attached as Exhibit G is a chronology briefly describing the significant activities and dates with respect to Fresenius' efforts to seek approval of VOLUVEN®.

§1.740(a)(12): *A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.*

Applicant believes that the '108 Patent is eligible for an extension pursuant to 35 U.S.C. 156(a) and the applicable provisions of 37 C.F.R. 1.710 *et seq.* Using calculations made in accordance with 37 C.F.R. 1.775, the '108 Patent is entitled to a term extension of 1,371 days (the "Term Extension Period"). The Term Extension Period was determined as follows:

#### Length of Regulatory Review Period

Under section 1.775(c), the length of the regulatory review period is 2,439 days, representing the sum of (1) the number of days in the period beginning on the effective date of the IND (April 24, 2001) and ending on the day before the Submission Date of the NDA (February 27, 2007) (2,136 days) and (2) the number of days in the period beginning on the Submission Date of the NDA (February 28, 2007) and ending on the date that the Product's NDA was approved (December 27, 2007) (303 days).

#### Length of Patent Term Extension

Under 1.775(d), a total of 1,068 days were subtracted from the 2,439 day length of the Regulatory Review Period, as follows:

- (i) 0 days were prior to the date on which the '108 Patent issued;
- (ii) 0 days during which the applicant did not act with due diligence; and
- (iii) 1,068 days representing one-half the number of days (2,136 days) remaining in the period defined by paragraph (c)(1) after which a total of 0 days were subtracted in accordance with paragraphs (d)(1)(i) and (d)(1)(ii).

Thus, the period calculated under section 1.775(d)(1) is 1,371 days.

The period calculated under section 1.775(d)(2), by adding 1,371 days to the original expiration date of the '108 patent (July 8, 2010), ends on April 9, 2014.

The period calculated under section 1.775(d)(3), by adding 14 years to the date of approval of the application under section 505 of the Federal Food Drug and Cosmetics Act, ends on December 27, 2021.

The date selected under section 1.775(d)(4), by comparing the two dates and selecting the earlier, is April 9, 2014.

Because the '108 Patent issued after September 24, 1984, the date determined under section 1.775(d)(5) is arrived at by adding 5 years to the original expiration date of the '108 Patent (July 8, 2015), and comparing that date (July 8, 2015) to the date determined under section 1.775(d)(4), results in selection of April 9, 2014 as the earlier date and thus the date to which the term of the '108 Patent should be extended.

§1.740(a)(13): *A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.*

Applicant, through the undersigned representative, hereby acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

§1.740(a)(14): *The prescribed fee for receiving and acting upon the application for extension.*

The prescribed fee for receiving and acting upon this application is \$1,120.00. A check in this amount is submitted with this application. Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 08-0380. A copy of this letter is enclosed for accounting purposes.

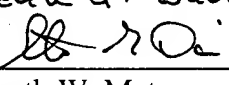
§1.740(a)(15): *The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.*

Please direct all inquiries and correspondence relating to this application for patent term extension to:

Brian T. Moriarty, Esq.  
Elizabeth W. Mata, Esq.  
Customer No.: 021005.  
Hamilton, Brook, Smith & Reynolds, P.C.  
530 Virginia Road  
P.O. Box 9133  
Concord, MA 01742  
Tel: (978) 341-0036

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

Steven G. Davis for Elizabeth W. Mata  
By  Registration No. 38,652  
Elizabeth W. Mata  
Registration No. 38,236  
Telephone: (978) 341-0036  
Facsimile: (978) 341-0136

Concord, MA 01742-9133  
Dated: February 21, 2008

SCHEDULE OF EXHIBITS

|           |  |
|-----------|--|
| Exhibit A | Ownership Records  |
| Exhibit B | Package Insert   |
| Exhibit C | Approval Letter dated December 27, 2007                    |
| Exhibit D | U.S. Patent No. 5,218,108                                  |
| Exhibit E | USPTO Maintenance Fee Record for U.S. Patent No. 5,218,108 |
| Exhibit F | Document Indicating Commencement of Phase III Trial        |
| Exhibit G | Chronology regarding VOLUVEN®                              |

Exhibit A:

1. Copy of executed assignment from inventors Klaus Sommermeyer, Franz Cech, Burghard Weidler, and Klaus Henning to Fresenius Aktiengesellschaft (AKA Fresenius AG), recorded in the United States Patent and Trademark Office on Reel 005345, Frames 0989 through 0992.
2. Copy of executed confirmatory assignment from Fresenius Aktiengesellschaft to Fresenius Kabi Deutschland GmbH (AKA Fresenius Kabi)

ASSIGNMENT

U.S. 11/533234

WHEREAS, We Dr. K. Sommermeyer,  
Dr. F. Cech, Dr. K. Henning and                       
Dr. B. Weidler, are the joint inventors of                       
                    , application for United States Letters Patent  
which is executed of even date herewith; and

WHEREAS, FRESENIUS AG, D-6380 Bad Homburg v.d.H., a  
corporation created and existing under and by virtue of the laws of the  
State and/or Country of the Federal Republik of Germany, is  
desirous of acquiring the entire right, title and interest in and to the  
aforesaid invention throughout the world, and all right, title and  
interest in, to and under any and all Letters Patent of the United States  
and all other countries throughout the world;

NOW, THEREFORE, for and in consideration of the sum of One Dollar  
(\$1.00) to us in hand paid by FRESENIUS AG  
and for other good and valuable considerations, the receipt of which is  
hereby acknowledged, we hereby sell, assign, transfer and set over to  
FRESENIUS AG, all right, title and  
interest in and to the said invention throughout the world, and said  
application for U.S. Letters Patent, and any and all divisions,  
continuations, and reissues thereof, and any and all Letters Patent of  
the United States and foreign countries which may be granted therefor,  
the same to be held and enjoyed by FRESENIUS AG  
                     for its own use and benefit, and for the  
use and benefit of its successors, assigns, or other legal  
representatives, to the end of the term or terms for which said Letters  
Patent of the United States or foreign countries are or may be granted or  
reissued, as fully and entirely as the same would have been held and  
enjoyed by us if this assignment and sale had not been made.

And we hereby authorize and request the Commissioner of Patents and  
Trademarks to issue any and all Letters Patent of the United States on  
said invention or resulting from said application and from any and all  
divisions, continuations, and reissues thereof, to FRESENIUS AG

REF 5345 FRAME 990

\_\_\_\_\_, as assignee of our entire interest, and hereby covenant that we have the full right to convey the entire interest herein assigned, and that we have not executed and will not execute any agreement in conflict herewith.

And we further hereby covenant and agree that we will, at any time, upon request, execute and deliver any and all papers that may be necessary or desirable to perfect the title of said invention and to such Letters Patent as may be granted therefor, to FRESENIUS AG

\_\_\_\_\_, its successors, assigns, or other legal representatives and that if FRESENIUS AG

\_\_\_\_\_, its successors, assigns or other legal representatives shall desire to file any divisional or continuation applications or to secure a reissue of such Letters Patent, or to file a disclaimer relating thereto, will upon request, sign all papers, make all rightful oaths and do all lawful acts requisite for the filing of such divisional or continuation application, or such application for reissue and the procuring thereof, and for the filing of such disclaimer, without further compensation but at the expense of said assignee, its successors, or other legal representatives.

And we do further covenant and agree that we will, at any time upon request, communicate to FRESENIUS AG, its successors, assigns or other legal representatives, such facts relating to said invention and Letters Patent or the file history thereof as may be known to me, and testify as to the same in any interference or other litigation when requested so to do, without further compensation but at the expense of said assignee, its successors, or other legal representatives.

EXECUTED THIS 25 day of April, 1990.

Signature \_\_\_\_\_

Dr. K. Sommermeier

EXECUTED THIS 25 day of April, 1990.

Signature \_\_\_\_\_

Dr. F. Cech

REEL 5345 FRAME 991

EXECUTED THIS 26 day of April, 1990.

Signature X

Dr. B. Weidler

EXECUTED THIS 25 day of April, 1990.

Signature Ula, Henning

Dr. K. Henning

REEL 5345 FRAME 992

RECORDED  
PATENT AND TRADEMARK  
OFFICE

JUN 5 1990

CONFIRMATORY ASSIGNMENT

Whereas, by virtue of an Assignment recorded in the United States Patent and Trademark Office on Reel 005345, Frames 0989 through 0992, Fresenius Aktiengesellschaft (hereinafter "Assignor") of Else-Kroener-Strasse 1, 61352 Bad Homburg v.d.H., Germany, was the owner of United States Letters Patent No. 5,218,108, issued June 8, 1993 (hereinafter "Patent").

Whereas, Fresenius Kabi Deutschland GmbH (hereinafter "Assignee"), a German corporation, of Else-Kroener-Strasse 1, 61352 Bad Homburg v.d.H., Germany, was desirous of acquiring from Assignor, an interest in, to and under the aforesaid Patent and the invention therein described and claimed, and in accordance with an agreement executed June 9, 1999 (hereinafter "Agreement"), Assignee acquired from Assignor all of its right, title and interest in the Patent in return for certain obligations to Assignor.

Now, therefore, Assignor hereby confirms that for good and valuable consideration, the receipt of which was hereby acknowledged in the Agreement, it has sold, transferred and conveyed to Assignee its entire right, title and interest in, to and under said Patent, to the full end of the term for which Letters Patent were granted, and any continuations, reissues, or extensions thereof and the invention therein described and claimed, including all claims, if any, which may have arisen for infringement of the Patent prior to the date of this confirmatory assignment.

Assignor further agrees that Assignor will, without demanding any further consideration therefor, at the request but at the expense of Assignee, do all lawful and just acts, including the execution and acknowledgment of instruments, that may be or become necessary for obtaining, sustaining, or reissuing the Patent, and for maintaining and perfecting Assignee's right, its

successors, assigns and legal representatives, to the Patent and any continuations, reissues or extensions thereof, and preliminary or other statements and the giving of testimony in any interference or other proceeding in which said invention or any application or patent directed thereto may be involved.

Fresenius Aktiengesellschaft

By B. Staude

Print Name: I.V. Elgit Staude  
Patent Manager

Title

Date February 18, 2008

Witness Signature S. Calabro - Folchert

Print Witness Name I.V. Dr. Silvano Calabro-Folchert  
Patent Manager

Address Frederstr. 41

35428 Langgöns

Witness Signature [Signature]

Print Witness Name Stefan Weiß

Address Hofedeweg 1

60320 Frankfurt

## NON ANNOTATED VERSION

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Voluven® safely and effectively. See full prescribing information for Voluven®.

**Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection)**

**For administration by intravenous infusion.**

**Initial U.S. Approval: To be determined**

### INDICATIONS AND USAGE

Voluven® is a plasma volume substitute indicated for the treatment and prophylaxis of hypovolemia. (1)

### DOSAGE AND ADMINISTRATION

**Administer by intravenous infusion only.**

- Daily dose and rate of infusion depend on the patient's blood loss, hemodynamics and on the hemodilution effects. (2)
- Initiate infusion slowly due to possible anaphylactoid reactions (2, 5.1)
- See full prescribing information for pediatric administration (2.2, 8.4)

### DOSAGE FORMS AND STRENGTHS

500 mL **freeflex®** flexible plastic intravenous solution container. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection. (3)

### CONTRAINDICATIONS

- Known hypersensitivity to hydroxyethyl starch (4)
- Fluid overload e.g., pulmonary edema and congestive heart failure (4)
- Renal failure with oliguria or anuria not related to hypovolemia (4)
- Patients receiving dialysis (4)
- Severe hyponatremia or severe hyperchloremia (4)
- Intracranial bleeding (4)

### WARNINGS AND PRECAUTIONS

- Anaphylactoid and hypersensitivity reactions (5.1, 6)
- Avoid fluid overload; adjust dosage in patients with cardiac or renal dysfunction (5.1)
- In severe dehydration, a crystalloid solution should be given first (5.1)
- Observe caution in patients with severe liver disease or bleeding disorders (5.1)
- Monitor kidney function, fluid balance and serum electrolytes (5.2)
- Elevated serum amylase values may occur and interfere with the diagnosis of pancreatitis (5.3)
- High dosages may cause dilution of blood components (5.3)

#### **ADVERSE REACTIONS**

Anaphylactoid/hypersensitivity reactions can occur. Most common adverse reactions (incidence >1%) are pruritus, elevated serum amylase, hemodilution (resulting in dilution of blood components, e.g., coagulation factors and other plasma proteins, and in a decrease in hematocrit). (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Hospira Inc. at 1-800-441-4100 or electronically at [ProductComplaintsPP@hospira.com](mailto:ProductComplaintsPP@hospira.com) or FDA at 1-800-FDA-1088 or electronically at [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### **DRUG INTERACTIONS**

No interactions with other drugs or nutritional products are known. (7)  
The safety and compatibility of additives have not been established.

#### **USE IN SPECIFIC POPULATIONS**

- Pediatric patients: Dosage should be adjusted to individual patient needs. (2.2, 8.4)
- Renal impaired or geriatric patients: Use care in dosage selection. (8.6)

**After reviewing the Highlights section, please read the following full prescribing information for this drug.**

See 17 for PATIENT COUNSELING INFORMATION  
**Labeling Revision Date:** TBD

*Draft: 2007/12/18*

---

## **FULL PRESCRIBING INFORMATION: CONTENTS\***

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- 2 DOSAGE AND ADMINISTRATION**
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  - 2.3 Directions for Use of Voluven®
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
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\*Sections of subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Voluven<sup>®</sup> (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) is indicated for the treatment and prophylaxis of hypovolemia.

It is not a substitute for red blood cells or coagulation factors in plasma.

### 2 DOSAGE AND ADMINISTRATION

Voluven<sup>®</sup> is administered by intravenous infusion only. The daily dose and rate of infusion depend on the patient's blood loss, on the maintenance or restoration of hemodynamics and on the hemodilution (dilution effect). Voluven<sup>®</sup> can be administered repetitively over several days. [see *Warnings and Precautions* (5)]

The initial 10 to 20 mL should be infused slowly, keeping the patient under close observation due to possible anaphylactoid reactions. [see *General Warnings and Precautions* (5.1)]

#### 2.1 Adult Dose

Up to 50 mL of Voluven<sup>®</sup> per kg of body weight per day (equivalent to 3 g hydroxyethyl starch and 7.7 mEq sodium per kg of body weight). This dose is equivalent to 3500 mL of Voluven<sup>®</sup> for a 70 kg patient.

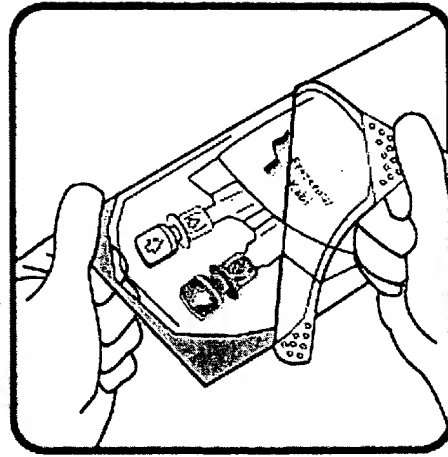
#### 2.2 Pediatric Dose

Limited clinical data on the use of Voluven<sup>®</sup> in children are available. In 41 children including newborns to infants (< 2 years), a mean dose of  $16 \pm 9$  mL/kg was administered. The dosage in children should be adapted to the individual patient colloid needs, taking into account the disease state, as well as the hemodynamic and hydration status. The safety and efficacy of Voluven<sup>®</sup> have not been established in the age group of 2 to 12 years. Use of Voluven<sup>®</sup> in children > 12 years is supported by evidence from adequate and well-controlled studies of Voluven<sup>®</sup> in adults and by data from children < 2 years old. [see *Pediatric Use* (8.4)]

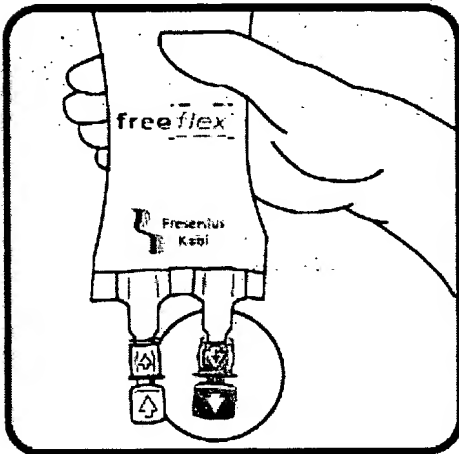
#### 2.3 Directions for Use of Voluven<sup>®</sup>



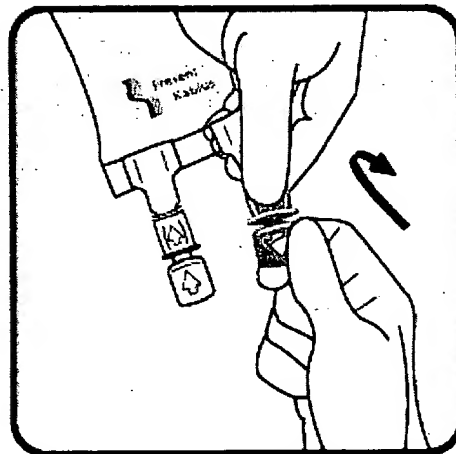
- Check the solution composition, lot number and expiry date, inspect the container for damage or leakage, if damaged do not use.



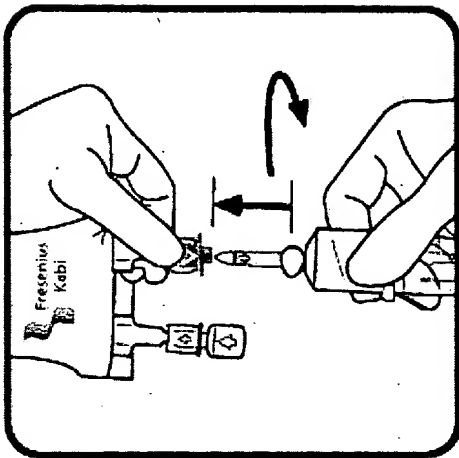
- Use opening aid to remove over-wrap.



- Identify the blue infusion (administration) port.



- Break off the blue tamper-evident cover from the freeflex<sup>®</sup> infusion port.



- Hang the bag on the infusion stand. Press drip chamber to get fluid level. Prime infusion set. Connect and adjust the flow rate.

- Close roller clamp. Insert the spike until the clear plastic collar of the port meets the shoulder of the spike.
  - Use a non-vented standard infusion set and close air inlet.
1. Do not remove the **freeflex**<sup>®</sup> IV container from its overwrap until immediately before use.
  2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
  3. Do not administer unless the solution is clear, free from particles and the **freeflex**<sup>®</sup> IV container is undamaged.
  4. Voluven<sup>®</sup> should be used immediately after insertion of the administration set.
  5. Do not vent.
  6. If administered by pressure infusion, air should be withdrawn or expelled from the bag through the medication/administration port prior to infusion.
  7. Discontinue the infusion if an adverse reaction occurs.
  8. It is recommended that administration sets be changed at least once every 24 hours.
  9. For single use only. Discard unused portion.

### **INCOMPATIBILITIES**

The safety and compatibility of additives have not been established.

### **3 DOSAGE FORMS AND STRENGTHS**

500 mL **freeflex**<sup>®</sup> flexible plastic intravenous solution container are available. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection.

#### **4 CONTRAINDICATIONS**

The use of Voluven<sup>®</sup> is contraindicated in the following conditions:

- known hypersensitivity to hydroxyethyl starch [see *General Warnings and Precautions (5.1)*]
- fluid overload (hyperhydration) and especially in cases of pulmonary edema and congestive heart failure
- renal failure with oliguria or anuria not related to hypovolemia
- patients receiving dialysis treatment
- severe hyponatremia or severe hyperchloremia
- intracranial bleeding.

#### **5 WARNINGS AND PRECAUTIONS**

##### **5.1 General Warnings and Precautions**

Anaphylactoid reactions (mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema) have been reported with solutions containing hydroxyethyl starch. If a hypersensitivity reaction occurs, administration of the drug should be discontinued immediately and the appropriate treatment and supportive measures should be undertaken until symptoms have resolved. [see *Adverse Reactions (6)*]

Fluid status and rate of infusion should be assessed regularly during treatment, especially in patients with cardiac insufficiency or severe kidney dysfunction.

In cases of severe dehydration, a crystalloid solution should be given first. Generally, sufficient fluid should be administered in order to avoid dehydration.

Caution should be observed before administering Voluven<sup>®</sup> to patients with severe liver disease or severe bleeding disorders (e.g., severe cases of von Willebrand's disease).

##### **5.2 Monitoring: Laboratory Tests**

Clinical evaluation and periodic laboratory determinations are necessary to monitor fluid balance, electrolyte concentrations, kidney function, acid-base balance, and coagulation parameters during prolonged parenteral therapy or whenever the patient's condition warrants such evaluation.

##### **5.3 Interference with Laboratory Tests**

Elevated serum amylase levels may be observed temporarily following administration of the product and can interfere with the diagnosis of pancreatitis.

At high dosages the dilutional effects may result in decreased levels of coagulation factors and other plasma proteins and a decrease in hematocrit.

## 6 ADVERSE REACTIONS

### 6.1 Overall Adverse Reaction Profile

From the accumulated clinical development experience, expected adverse reactions after administration of Voluven® occurring in less than 10% of patients are as follows:

*Immune system disorders (Rare, >0.01% to <0.1%):* Products containing hydroxyethyl starch may lead to anaphylactoid reactions (hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema). In the event of an intolerance reaction, the infusion should be discontinued immediately and the appropriate emergency medical treatment initiated. [see *General Warnings and Precautions* (5.1)]

*Skin and subcutaneous tissue disorders (Common, >1 to <10%, dose dependent):* Prolonged administration of high dosages of hydroxyethyl starch may cause pruritus (itching) which is an undesirable effect observed with all hydroxyethyl starches.

*Investigations (Common, >1% to <10%, dose dependent):* The concentration of serum amylase can rise during administration of hydroxyethyl starch and can confound the diagnosis of pancreatitis. At high doses the dilutional effects may result in decreased levels of coagulation factors and other plasma proteins and in a decrease of hematocrit. [see *Interference with Laboratory Tests* (5.3)]

### 6.2 Adverse Reactions in Clinical Trials

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug may not reflect the rates observed in practice.

During clinical development, 471 patients were exposed to Voluven®, and a total of 768 patients received the hydroxyethyl starch 130/0.4 drug substance contained in Voluven® at different concentrations (2%, 4%, 6%, or 10%) and at cumulative doses of several mL up to 66 L<sup>1)</sup>. The mean duration of treatment with hydroxyethyl starch 130/0.4 was  $3.9 \pm 3.3$  days, mean cumulative doses were  $3338 \pm 3695$  mL, and the longest follow-up period was 90 days.

In the US trial, 100 patients undergoing elective orthopedic surgery were treated either with Voluven® (N=49) or hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) (N=51) for intraoperative volume replacement. Mean infusion volumes were  $1613 \pm 778$  mL for Voluven® and  $1584 \pm 958$  mL for hetastarch.

*Adverse reactions observed in at least 1% of patients:* In the US trial comparing Voluven® with hetastarch, a possible relationship to Voluven® was reported in five cases in a total of three patients (aPTT elevated, PT prolonged, wound hemorrhage, anemia, pruritus). A possible relationship to hetastarch was reported in five patients (three cases of coagulopathy; two cases of pruritus). The three coagulopathy cases in the hetastarch group were serious and occurred in patients receiving more than the labeled ceiling dose (20 mL/kg), whereas no serious coagulopathy occurred in the Voluven® group.

### **6.3 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of Voluven® and other types of hydroxyethyl starch solutions. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The safety profile from postmarketing experience of Voluven® is not different from the profile obtained from clinical trials performed using the product.

Based on spontaneous reporting of hypersensitivity reactions, urticaria, bronchospasm, or hypotension were the most frequently reported serious adverse drug reactions for patients treated with Voluven®.

With the administration of hydroxyethyl starch solutions, disturbances of blood coagulation can occur depending on the dosage<sup>2)</sup>.

## **7 DRUG INTERACTIONS**

No interactions with other drugs or nutritional products are known.

The safety and compatibility of other additives have not been established [see *Directions for Use of Voluven®* (2.3)].

## **8 USE IN SPECIAL POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C. Voluven® has been shown to cause embryocidal or other adverse effects in rats and rabbits when given in doses 1.7 times the human dose. There are no adequate and well-controlled studies in pregnant women. Voluven® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The type of hydroxyethyl starch present in Voluven® had no teratogenic properties in rats or rabbits. At 5 g/kg of body weight per day, administered as a bolus injection, fetal retardations and embryo-lethal effects were observed in rats and rabbits, respectively. In rats, a bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. All adverse effects were seen exclusively at maternal toxic doses due to fluid overload. [see *Toxicology* (13.2.1)]

Fertility studies on directly exposed animals have not been conducted.

### **8.2 Labor and Delivery**

Information on the use of Voluven® during labor or delivery is unknown.

### **8.3 Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Voluven® is administered to a nursing woman.

### **8.4 Pediatric Use**

In one trial, children including newborns to infants (< 2 years) undergoing elective surgery were randomized to receive Voluven® (N=41) or 5% albumin (N=41). The mean dose of Voluven® administered was  $16 \pm 9$  mL/kg<sup>3)</sup>.

Voluven® may be given to premature infants and newborns only after a careful risk/benefit evaluation. The safety and efficacy of Voluven® have not been established in the age group of 2 to 12 years. Use of Voluven® in children > 12 years is supported by evidence from adequate and well-controlled studies of Voluven® in adults and by data from children < 2 years old. Dosage in children should be adapted to individual patient colloid needs, taking into account underlying disease, hemodynamics and hydration status. [see *Pediatric Dose* (2.2)]

#### **8.5 Geriatric Use**

Of the total number of subjects in clinical studies of Voluven® (N= 471), 32% were 65 years old and older while 7% were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

#### **8.6 Renal impairment**

Voluven® is mainly excreted by the kidneys, and the risk of adverse reactions may be greater in patients with impaired renal function. Volume status, infusion rate, and urine output should be closely monitored. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. [see *Pharmacokinetics* (12.3)]

### **9 DRUG ABUSE AND DEPENDENCE**

Voluven® is not considered to be a drug of abuse potential.

### **10 OVERDOSAGE**

As with all plasma volume substitutes, overdosage can lead to overloading of the circulatory system (e.g. pulmonary edema). In this case, the infusion should be stopped immediately and if necessary, a diuretic should be administered. [see *General Warnings and Precautions* (5.1)]

### **11 DESCRIPTION**

Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) is a clear to slightly opalescent, colorless to slightly yellow, sterile, non-pyrogenic, isotonic solution for intravenous administration using sterile equipment.

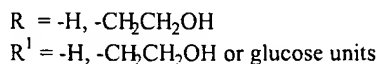
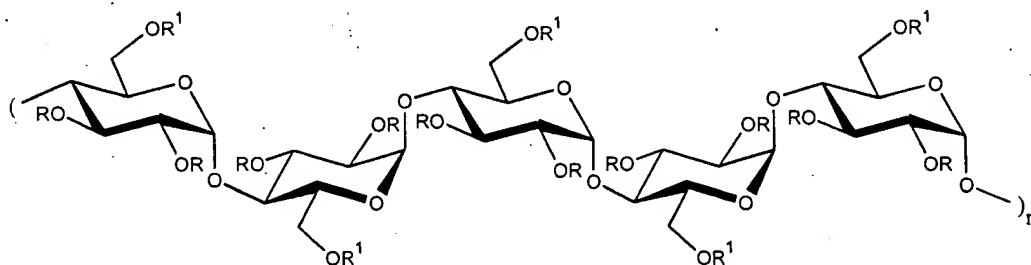
Each 100 mL of the solution contains:

|                             |        |
|-----------------------------|--------|
| Hydroxyethyl Starch 130/0.4 | 6 g    |
| Sodium Chloride USP         | 900 mg |
| in Water for Injection USP  |        |

pH adjusted with Sodium Hydroxide USP  
or Hydrochloric Acid USP

Electrolytes (mEq/L): Sodium 154, Chloride 154. pH 4 to 5.5. Calculated osmolarity 308 mOsmol/L.

The hydroxyethyl starch contained in Voluven® is a synthetic colloid for use in plasma volume replacement. The chemical name of hydroxyethyl starch is poly(O-2-hydroxyethyl) starch. The structural formula of hydroxyethyl starch is



Voluven® is packaged in 500 mL flexible plastic containers (**freeflex**®). **Freeflex**® is a flexible container made from coextruded polyolefin and is free of PVC, plasticizers, adhesives or latex (Non-DEHP, Latex-free). The **freeflex**® container offers an air-closed system and can be used with non-vented IV sets which prevent external air contamination. **Freeflex**® is collapsible and can be used in emergency cases for pressure infusion.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Voluven® contains hydroxyethyl starch in a colloidal solution which expands plasma volume when administered intravenously. This effect depends on the mean molecular weight (130,000 daltons; range 110,000 – 150,000 daltons), the molar substitution by hydroxyethyl groups (0.4; range 0.38 – 0.45) on glucose units of the starch, the pattern of hydroxyethyl substitution (C<sub>2</sub>/C<sub>6</sub> ratio) of approximately 9:1, and the concentration (6%), as well as the dosage and infusion rate.

Hydroxyethyl starch is a derivative of thin boiling waxy corn starch, which mainly consists of a glucose polymer (amylopectin) predominately composed of α-1-4-connected glucose units with several α-1-6-branches. Substitution of hydroxyethyl groups on the glucose units of the polymer reduces the normal degradation of amylopectin by α-amylase in the body. The low molar substitution (0.4) is the main pharmacological determinant for the beneficial effects of Voluven® on pharmacokinetics, intravascular volume and hemodilution<sup>4</sup>. To describe the molecular weight and molar substitution characteristics of the hydroxyethyl starch in Voluven®, the compound is designated as hydroxyethyl starch 130/0.4.

## 12.2 Pharmacodynamics

After isovolemic exchange of blood with 500 mL of Voluven® in healthy volunteers, blood volume is maintained for at least 6 hours.

## 12.3 Pharmacokinetics

The pharmacokinetic profile of hydroxyethyl starch is complex and largely dependent on its molar substitution as well as its molecular weight<sup>4)</sup>. When administered intravenously, molecules smaller than the renal threshold (60,000-70,000 daltons) are readily and rapidly excreted in the urine, while molecules with higher molecular weights are metabolized by plasma  $\alpha$ -amylase prior to excretion via the renal route.

The mean *in vivo* molecular weight of Voluven® in plasma is 70,000 – 80,000 daltons immediately following infusion and remains above the renal threshold throughout the treatment period.

Following intravenous administration of 500 mL Voluven® to healthy volunteers, plasma levels of Voluven® remain at 75% of peak concentration at 30 minutes post-infusion and decrease to 14% at 6 hours post-infusion. Plasma levels of Voluven® return to baseline levels 24 hours following infusion. Plasma clearance, volume of distribution, and elimination half-life of Voluven® in healthy volunteers following IV administration of 500 mL were 31.4 mL/min, 5.9 liters, and 12 hours, respectively. Approximately 62 % of Voluven® was excreted as hydroxyethyl starch molecules in urine within 72 hours.

The pharmacokinetics of Voluven® are similar following single and multiple dose administration. No significant plasma accumulation occurred after daily administration of 500 mL of a 10% solution containing hydroxyethyl starch 130/0.4 over a period of 10 days. Approximately 70% of Voluven was excreted as hydroxyethyl starch molecules in urine within 72 hours.

### Renal Impairment:

Following a single intravenous administration of Voluven® (500 mL) in subjects with varying degrees of renal dysfunction, the AUC and clearance of Voluven® increased by 73% and decreased by 42% in patients, respectively, with creatinine clearance <50 mL/min as compared to patients with creatinine clearance >50 mL/min. However, terminal half-life and peak hydroxyethyl starch concentration were not affected by renal impairment. Plasma levels of Voluven® returned to baseline levels 24 hours following infusion. Approximately 59 % and 51 % of Voluven® were excreted as hydroxyethyl starch molecules in urine within 72 hours in patients with creatinine clearance  $\geq 30$  mL/min and <30 mL/min, respectively.

There are no data available on the use of Voluven® in patients undergoing hemodialysis.

Pharmacokinetic data in patients with hepatic insufficiency or in pediatric or geriatric patients are not available. Effects of gender or race on the pharmacokinetics of Voluven® have not been studied.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies in animals to evaluate the carcinogenic potential of Voluven® have not been performed. No mutagenic effects were observed with hydroxyethyl starch 130/0.4 10% solution in the following tests on mutagenic activity: *Salmonella typhimurium* reverse mutation assay (*in vitro*), mammalian cells in the *in vitro* gene mutation assay, assessment of the clastogenic activity in cultured human peripheral lymphocytes (*in vitro*), bone marrow cytogenetic test in Sprague-Dawley rats.

Fertility studies on directly exposed animals have not been performed.

### **13.2 Animal Toxicology and Pharmacology**

#### **13.2.1 Toxicology**

Three-month repeat infusion toxicology studies were conducted in rats and dogs in which three groups of animals were administered daily intravenous infusion over three hours. Dosing volumes of either 60 or 90 mL/kg body weight of hydroxyethyl starch 130/0.4 (10% solution) or 90 mL/kg 0.9% sodium chloride injection were studied. Observed toxicity following repeat infusion of hydroxyethyl starch is consistent with the oncotic properties of the solution resulting in hypervolemia in the animals. There were no apparent gender-related effects on toxicity following repeat administration of hydroxyethyl starch 130/0.4 in rats or dogs.

In reproduction studies in rats and rabbits, hydroxyethyl starch 130/0.4 (10% solution) had no teratogenic properties. Embryo-lethal effects were observed in rabbits at 5 g/kg body weight/day. In rats, bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. Signs of fluid overload were seen in the dams. Hydroxyethyl starch 130/0.4 (10% solution) was observed to have no effect in studies assessing skin sensitization, antigenicity, and blood compatibility.

#### **13.2.2 Pharmacology**

The pharmacodynamic effect of Voluven® was examined in a hemorrhagic shock model in conscious rats and a hemodilution model in dogs. In both studies the control group received pentastarch (6% hydroxyethyl starch 200/0.5).

Voluven® was as effective as pentastarch in maintaining cardiopulmonary function during isovolemic hemodilution in beagle dogs. In the three-hour follow-up period no additional administration of colloid was necessary.

There were no differences in long-term survival of rats after a single administration of Voluven® and pentastarch solutions following induced hemorrhagic shock (67% and 50% blood loss). In the 67% induced bleeding group receiving Voluven® (N=6), the survival rate was 83% which is within the normal range for this type of experiment. In the corresponding pentastarch group, survival was 100%. Infusion of Ringer's lactate resulted in a 50% survival rate after a 50% blood loss and a 0% survival after a 67% blood loss.

After multiple intravenous infusions of 0.7 g per kg body weight per day of 10% hydroxyethyl starch 130/0.4 or 10% hydroxyethyl starch 200/0.5 solution during 18 consecutive days, the plasma hydroxyethyl starch concentration in rats treated with hydroxyethyl starch 130/0.4 was lower compared to rats treated with hydroxyethyl starch 200/0.5. Hydroxyethyl starch 130/0.4 was eliminated faster than hydroxyethyl starch 200/0.5. In both groups, clear signs of hydroxyethyl starch tissue storage were detected in lymph nodes and spleen. Numerous empty vacuoles in macrophages were observed. Only minimal cellular vacuolization was found in the liver and kidney. Histochemical differences between the groups were not observed.

A study with 10% radiolabeled <sup>14</sup>C-hydroxyethyl starch 130/0.4 and 10% <sup>14</sup>C-hydroxyethyl starch 200/0.5 solutions was carried out<sup>6)</sup>. In animals treated with hydroxyethyl starch 130/0.4, radioactivity decreased from 4.3% of the total administered dose (2.6 g hydroxyethyl starch 130/0.4 per animal) on day 3 to 0.65% on day 52. In animals treated with hydroxyethyl starch 200/0.5, the <sup>14</sup>C-activity decreased from 7.7% of the total administered dose (2.7 g hydroxyethyl starch 200/0.5 per animal) on day 3 to 2.45% on day 52. These results confirm the faster elimination and lower persistence of hydroxyethyl starch 130/0.4 in tissue.

## 14 CLINICAL STUDIES

Voluven® was studied in controlled clinical trials in adult and pediatric surgical patients and in patients in intensive care units. Clinical studies included patients undergoing various types of surgery (orthopedic, urologic, cardiac) and trauma intensive care for situations in which hypovolemia is treated (pre-, intra-, and postoperative) or prevented (autologous blood donation, acute normovolemic hemodilution, hypervolemic hemodilution before cardiac surgery). The safety and efficacy of Voluven® were compared to other colloidal plasma substitutes [pentastarch (6% hydroxyethyl starch 200/0.5), hetastarch (6% hydroxyethyl starch 450/0.7), gelatin solution or human serum albumin] in studies carried out in common clinical settings of volume replacement therapy. Perioperative fluid administration of Voluven® ranged from 500 to 4500 mL/day in surgical patients, and cumulatively, 6 to 66 L during stays in intensive care units following traumatic brain injury.

A prospective, controlled, randomized, double-blind, multi-center trial of 100 patients undergoing elective orthopedic surgery was conducted in the US evaluating Voluven® (N=49) compared to hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) (N=51) for intraoperative volume replacement therapy<sup>7)</sup>. The primary efficacy variable, total volume of colloid solution required for intraoperative volume replacement therapy, was equivalent for the two treatment groups. Mean volume infused was 1613 ± 778 mL for Voluven® and 1584 ± 958.4 mL for hetastarch. The ratio Voluven®/hetastarch was estimated as 1.024 with a 95%

confidence interval (0.84, 1.25), which was included within the equivalence range of (0.55, 1.82) prespecified in the study protocol. This indicated that Voluven® and hetastarch have similar efficacy as intraoperative volume replacement therapy in major orthopedic surgery.

A second objective of the trial was to show superiority for safety between Voluven® and hetastarch. Four safety endpoints were prospectively defined and compared in a sequential manner (in order to preserve the type-I error rate, i.e., observing a difference where none actually exists). Per protocol, if there was no difference found between treatment arms for the first safety endpoint (EBL), the remaining endpoints were to be considered exploratory analyses requiring additional studies for confirmation.

Overall, no significant differences in serious adverse events were noted between the two treatment arms, but three cases of serious coagulopathy occurred in the hetastarch treatment arm. All three subjects received high doses (>3000 mL; labeled ceiling dose = 20 mL/Kg) of the product, which are known to increase the risk of bleeding. Since EBL for the two treatment arms was not statistically different (95% confidence interval includes unity), the difference observed for Factor VIII (see table, below) must be interpreted with caution. An exploratory analysis of total erythrocyte volume transfused (8.0 mL/kg vs. 13.8 mL/kg, Voluven® vs hetastarch, respectively) must also be viewed with caution.

**Table: Safety Variables for Study HS-13-30-US**

| Variable                           | Mean            |                    | Ratio VOLUVEN/Hetastarch |                |
|------------------------------------|-----------------|--------------------|--------------------------|----------------|
|                                    | VOLUVEN<br>N=49 | Hetastarch<br>N=51 | Estimate                 | 95% CI         |
| Calculated red blood cell loss [L] | 1.17            | 1.31               | 0.910                    | [0.720; 1.141] |
| Factor VIII [%]*                   | 100.5           | 81.4               | 1.244                    | [1.000; 1.563] |
| von Willebrand factor [%]*         | 97.7            | 88.7               | 1.128                    | [0.991; 1.285] |
| Fresh frozen plasma [mL]*          | 72              | 144                | 0.723                    | [0.000; 2.437] |

\*Exploratory analyses

There was no statistically significant difference between the two treatment groups with respect to the secondary efficacy endpoints of hemodynamic stability, body temperature,

hemodynamic parameters, blood pressure, central venous pressure, heart rate, fibrinogen and platelet count.

In addition to the US trial, three non-US trials were conducted with the primary objective of showing equivalency (based on mean difference rather than mean ratio as in the US study) between Voluven® and pentastarch in maintaining or restoring hemodynamic parameters. The largest of the three trials (N=100) met the prespecified boundary (-500 mL, 500 mL), but the two smaller studies (N=52 and N=59) did not.

In exploratory analyses, the effect of Voluven® on coagulation parameters (von Willebrand factor, Factor VIII, and Ristocetin cofactor) was shown to be significantly lower than pentastarch at one or more time points (US and non-US trials). These findings are consistent with the lower molar substitution, lower average molecular weight and narrower molecular weight distribution of Voluven® as compared to pentastarch resulting in a lower *in vivo* molecular weight and increased elimination from the circulation.

A safety profile of Voluven® at least as favorable as for pentastarch was also demonstrated in studies where Voluven® was administered at doses higher (up to 50 mL/kg or 3 g/kg) than for pentastarch (up to 33 mL/kg or 2 g/kg) in clinical settings where large or repetitive doses are administered. [see *Adverse Reactions* (6)]

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- 4) Jungheinrich C, Neff T. Pharmacokinetics of hydroxyethyl starch. *Clin Pharmacokinetik* 2005; 44 (7): 681-699
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- 6) Leuschner J, Opitz J, Winkler A, Scharpf R, Bepperling F. Tissue storage of <sup>14</sup>C-labeled hydroxyethyl starch (HES) 130/0.4 and HES 200/0.5 after repeated intravenous administration to rats. *Drugs R D* 2003; 4 (6): 331-8

7) Gandhi SD, Weiskopf RB, Jungheinrich C et al. Volume replacement therapy during major orthopedic surgery using Voluven<sup>®</sup> (hydroxyethyl starch 130/0.4) or hetastarch. Anesthesiology 2007; 106:1120-1127

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

Voluven<sup>®</sup> (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) for intravenous infusion is supplied in the following primary container and carton sizes:

Polyolefin bag (*freeflex*<sup>®</sup>) with overwrap: 500 mL  
Carton of 15 x 500 mL  
NDC 0409-1029-01

Store at 15° to 25°C (59° to 77°F). Do not freeze.

## **17 PATIENT COUNSELING INFORMATION**

Because this product is not used directly by patients, patient counseling or instructions for use by patients is not considered necessary.

Manufactured by: Fresenius Kabi Norge AS,  
P.O. Box 430,  
NO-1753 HALDEN, NORWAY

Distributed by:  
Hospira, Inc.  
275 North Field Drive  
Lake Forest, Illinois 60045 USA

Made in Norway

EN-1597



## Product Approval Information - New Drug Applications

December 27, 2007

Our reference: NDA BN070012

Fresenius Kabi  
Attention: W. Gerald Cohn  
c/o Carolina Research Group, Inc.  
P.O. Box 32295  
Raleigh, NC 27622

Dear Mr. Cohn:

Please refer to your new drug application dated February 28, 2007 and received March 1, 2007, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for 6% Hydroxyethyl Starch in 0.9% Sodium Chloride Infusion (Voluven® 500 mL freeflex® flexible plastic intravenous solution container).

We acknowledge receipt of your submissions dated February 28; March 30; June 25 and 26; July 26; August 16 and 17; September 6 and 20; October 2, 4, 12, and 17; November 9, 14, 16, 27, and 30; and December 3 and 10, 2007

This new drug application provides for the use of 6% Hydroxyethyl Starch in 0.9% Sodium Chloride Infusion ((Voluven® 500 mL freeflex® flexible plastic intravenous solution container) for treatment and prophylaxis of hypovolemia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA BN070012.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

We remind you of your postmarketing study commitments in your submission dated November 30, 2007. The commitments are listed below.

1. To perform a multiple-dose randomized controlled trial (RCT) to be conducted in

subjects with severe sepsis including subjects with renal dysfunction and at risk for deterioration of renal dysfunction. Fresenius Kabi will submit the final Clinical Study Protocol of this Phase 3b study entitled "Crystalloids or colloids in patients with severe sepsis: effects on hemodynamics and tolerability of enteral nutrition" (Short title: CRYSTMAS, study code 06-HE06-01) within 3 months of the Approval Letter and will submit the final Clinical Study Report to FDA within 36 months of the Approval Letter.

Protocol Submission: by within 3 months of the date of this letter

Final Report Submission: by within 36 months of the date of this letter

2. Fresenius Kabi commits to perform a randomized controlled trial (RCT) to be conducted in children in the age group of 2 to 12 years. Fresenius Kabi will submit the final Clinical Study Protocol of this Phase 3 study entitled "Efficacy and safety of 6 % hydroxyethyl starch 130/0.4 ((Voluven®) vs 5% HSA in volume substitution therapy during open-heart surgery in 2 to 12 years old pediatric patients" within 12 months of the Approval Letter and will submit the final Clinical Study Report to FDA within 36 months of the Approval Letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Blood Applications and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Advertising and Promotional Labeling Branch (HFM-602)  
1401 Rockville Pike, Suite 200 North  
Rockville, MD 20852-1448

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm).

FDA has determined that referral of this application to the Blood Products Advisory Committee (BPAC) prior to approval (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]) was not needed for the following reasons: Voluven®'s mechanism of action as a plasma volume expander indicated for the treatment and prophylaxis of hypovolemia is well studied and understood. The European-approved Voluven® product manufactured by Fresenius Kabi has demonstrated comparable safety and efficacy with similar products, such as hetastarch and pentastarch. Studies to evaluate the efficacy of Voluven® were adequate and the results did not raise any concerns related to safety. Review of information submitted in the NDA for Voluven® did not raise any controversial issues or pose unanswered scientific questions which would have benefited from advisory committee discussion and recommendations.

If you have any questions, please contact Franklin T. Stephenson, Regulatory Project Manager, at (301) 827-6165.

Sincerely,

/signed/

Jay S Epstein, M.D.  
Director Office of Blood Research and Review  
Center for Biologics  
Evaluation and Research

Enclosure: Package Insert (PDF, 233 KB)

Updated: December 27, 2007



US005218108A

**United States Patent** [19]

Sommermeyer et al.

[11] Patent Number: 5,218,108

[45] Date of Patent: Jun. 8, 1993

[54] HYDROXYLETHYLSTARCH (HES) AS  
PLASMA EXPANDER AND PROCESS FOR  
PREPARING HES[75] Inventors: Klaus Sommermeyer; Franz Cech;  
Burghard Weidler, all of Rosbach;  
Klaus Henning, Usingen, all of Fed.  
Rep. of Germany[73] Assignee: Fresenius AG, Bad Homburg, Fed.  
Rep. of Germany

[21] Appl. No.: 533,294

[22] Filed: Jun. 5, 1990

[30] Foreign Application Priority Data

Jun. 16, 1989 [DE] Fed. Rep. of Germany ..... 3919729

[51] Int. Cl.<sup>5</sup> ..... C08B 31/10; A61K 31/72

[52] U.S. Cl. .... 536/111; 514/60

[58] Field of Search ..... 536/111; 514/60

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| 4,837,314 | 6/1989  | Eastman        | 536/111 |

## FOREIGN PATENT DOCUMENTS

935339 8/1963 United Kingdom

Primary Examiner—Nathan M. Nutter  
 Attorney, Agent, or Firm—Omri M. Behr; Matthew J.  
 McDonald

## [57] ABSTRACT

A hydroxyethyl starch for use as plasma expander which is obtainable by hydrolytic predegradation of a starch rich in amylopectin, partial hydroxyethylation to a specific substitution degree in the presence of alkali and subsequent hydrolytic degradation to a specific molecular weight, comprises a mean molecular weight of 60,000–600,000 and a substitution degree MS of 0.15–0.5. The ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8–20 and the substitution degree DS lies in the range from 0.15 to 0.5. A process for the preparation of this hydroxyethyl starch employs 2-chloroethanol as hydroxyethylation agent. The hydroxyethylation is carried out under alkaline conditions at room temperature, the pH value held at a value of about 12 and the temperature held at a value of about 20° C.

7 Claims, No Drawings

# HYDROXYLETHYLSTARCH (HES) AS PLASMA EXPANDER AND PROCESS FOR PREPARING HES

The field of volume substitution (e.g. hemorrhagic shock) or hemodilution (e.g. arterial occlusive disease, Fontaine II B, III) is today inconceivable without the use of colloidal plasma substitutes. For both these indications, of the exogeneous plasma substitutes (starch, gelatins, dextran), hydroxyethyl starch (HES) has found the greatest acceptance in recent years.

The lower disturbance of coagulation and the clearly reduced incidence of serious anaphylactoid reactions compared with dextran are responsible for the good acceptance of hydroxyethyl starch in the field of volume replacement and hemodilution. In addition, it has been possible to show that the volume efficacy of hydroxyethyl starch, depending on the indication, may be referred to as sufficient to good, a differentiated therapy being possible, depending on the state of the patient, by using the various known hydroxyethyl starch preparations differing in molecular weight and substitution degree. The factor considered particularly favourable here is the low colloid osmotic pressure of starch solutions compared with dextrans. With regard to the kidneys, the lower urine viscosity involves a lesser risk of a decrease in functional activity. In the area of hemodilution, in addition to the reduction of hematocrit, the reduction of plasma viscosity in particular has proved to be a therapeutically effective principle of HES-induced rheological improvement. Therapeutical advantages are obtained over other exogeneous plasma substitutes.

Already known hydroxyethyl starches used as plasma expanders have different molecular weights  $M_w$  and substitution degrees MS and DS as well as different substitution patterns.

Due to the use of the natural starting raw material amylopectin and the production process in which to a certain extent a cleaving of the polymer chains is necessary, the hydroxyethyl starch is not present as molecular unitary substance with defined molecular weight but as mixture of molecules of different size which are also differently substituted by hydroxyethyl groups. The characterization of such mixtures requires the aid of statistically determined magnitudes (cf. K. Sommermeyer et al., "Clinically employed hydroxyethyl starch: physical chemical characterization", *Krankenhauspharmazie*, 271 (1987)). To denote the average molecular weight, the mean molecular weight  $M_w$  is used. The general definition of this mean value is:

$$M_w = \frac{\sum_i N_i \cdot M_i^w}{\sum_i N_i \cdot M_i^{w-1}}$$

There are two differently defined substitution degrees for defining the substitution by hydroxyethyl groups.

The substitution degree MS (molar substitution) is defined as the average number of hydroxyethyl groups per anhydroglucose unit. It is determined from the total number of hydroxyethyl groups in a specimen, for example in accordance with Morgan, by ether splitting and subsequent quantitative determination of ethyl iodide and ethylene, which are thereby formed.

In contrast, the substitution degree DS (degree of substitution) is defined as the proportion of the substi-

tuted anhydroglucose units of all anhydroglucose units. It can be determined from the measured amount of the unsubstituted glucose after hydrolysis of a specimen. It follows from these definitions that  $MS > DS$ . In the case where only monosubstitution is present, i.e. each substituted anhydroglucose unit carries only one hydroxyethyl group,  $MS = DS$ .

It is known that  $\alpha$ -amylase breaks down hydroxyethyl starches in the sense that only glycosidic bonds of unsubstituted anhydroglucose units are split. It is further known that with increasing degree of substitution MS or DS the elimination of hydroxyethyl starches from the plasma is retarded.

It is moreover known that for the same MS, DS and the same molecular weight distribution starches substituted mainly in the 6-position are eliminated faster than starches substituted mainly in the 2-position.

In this respect, only hydroxyethyl starches having a low C2/C6 ratio or being highly substituted were used for pharmaceutical purposes.

Thus, GB-PS 1,395,777 describes hydroxyethyl starches substituted predominantly in 6-position corresponding to a C2/C6 ratio of 0.5 to 2.0. These hydroxyethyl starches are made by reaction of wax maize starch with ethylene oxide with alkali in excess.

DE-OS 2,814,032 describes a process for preparing hydroxyl starch suitable as blood plasma expander, the starch being alkaline hydroxyethylated, the reaction mixture then neutralized and the hydroxyethyl starch formed extracted from the reaction mixture with a solvent, such as dimethyl formamide in which the salts formed by the neutralization are only sparingly soluble or not soluble at all. The hydroxyethyl starch obtained has a molar ratio of 2-O-hydroxyethyl anhydroglucose to 6-O-hydroxyethyl anhydroglucose of about 1.

According to the process described in DE-OS 3,313,600 for preparing plasma expanders on a starch basis in which the degradation step of the starch rich in amylopectin is at least partially carried out enzymatically, the breaking down of the starch is performed to a molecular weight of 40,000 to 1,000,000 Dalton, in particular from 200,000 to 450,000 Dalton, and the etherification to a substitution degree (MS) of 0.1 to 0.8 or 0.5 to 0.8, in particular 0.5 to 0.7 (cf. page 8, paragraph 3). The ratio of the substitution of C2 compared with the substitution of C6 is low (cf. page 5, paragraph 2).

The aforementioned hydroxyethyl starches have the disadvantage that they do not ensure a complete degradability from the plasma within a period of about 6-12 hours and moreover, due to their high substitution degree MS ( $MS > 0.5$ ), involve the danger that with the usual repetition infusions over longer periods of time an accumulation of difficultly eliminatable components takes place in the serum and tissue. Due to this long-time storing, allergic reactions may occur, for example nettle rash, etc.

The problem underlying the invention is therefore to make available a hydroxyethyl starch which can be completely broken down within a physiologically reasonable time.

A further problem resides in making available an HES which nevertheless due to the choice of a suitable MS or DS value and the molecular weight has a controllable elimination behaviour.

The starting products for recovering hydroxyethyl starch are starches having a high content of amylopectin, the highly branched component of starch, in partic-

ular potato starch, wax maize starch, sorghum starch or waxy rice starch.

For a coarse presetting of the intended molecular weight these starches are subjected to a hydrolytic degradation reaction. The molecular weight is reduced here from about 20,000,000 Dalton to several million Dalton.

In the subsequent alkaline hydroxyethylation with known hydroxyethylation agents, it is possible to introduce a hydroxyethyl group into position 2, 3 and 6 of the anhydroglucose unit. Disubstituted units, such as 2,3-dihydroxyethyl anhydroglucose, 2,6-dihydroxyethyl anhydroglucose are formed in the synthesis with less probability. The reactivity of the individual hydroxy groups in the unsubstituted anhydroglucose unit compared with hydroxyethylation is different depending on the reaction conditions. Within certain limits, the substitution pattern, i.e. the individual differently substituted anhydroglucoses statistically shared amongst the individual polymer molecules, can thereby be influenced. Advantageously, predominantly the 2 and the 6-position is hydroxyethylated, the 6-position being preferred due to easier accessibility.

The objective of the present invention, that is the preparation of a hydroxyethyl starch which can be completely broken down within a physiologically reasonable period and which on the other hand nevertheless has a controllable elimination behaviour, is achieved by a starch substituted predominantly in 2-position and substituted as homogeneously as possible, MS being approximately equal to DS.

The predominant 2-substitution makes the hydroxyethyl starch relatively difficult to degrade for  $\alpha$ -amylase. It is advantageous to avoid as far as possible the occurrence of substituted anhydroglucose units one behind the other within the polymer molecule in order to guarantee complete degradability.

This can be achieved in that the substitution is accordingly low, enabling the molecules to derivate statistically in the sense of a substitution distributed over the total molecules. This results in substituted anhydroglucoses at a relatively large distance apart, compensating the effect of the retardation of the  $\alpha$ -amylase degradation due to the predominant 2-substitution and enabling a controllability of the degradation rate to be achieved.

It has been found that hydroxyethyl starches substituted extremely low ( $MS < 0.5$ ) and having a high ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units are rapidly and completely eliminated from the human body within the first hours of the infusion.

It has further been found that such hydroxyethyl starches, in spite of the low substitution, contrary to the opinion of those skilled in the art, do have an adequately high solubility in aqueous medium so that the solutions are stable even for relatively long periods of time and do not form any agglomerates or gels which would make the further use as plasma expander solution impossible.

Hydroxyethyl starches with the characteristics described above therefore combine the general advantages of hydroxyethyl starch compared with other plasma expander types, such as gelatins or dextran, and avoids the disadvantages of the hitherto known hydroxyethyl starch types used for the indications described.

Hydroxyethyl starches having the aforementioned properties can be obtained with the aid of a process including essentially the following steps:

a) Preextraction of the starch used with methanol to remove vegetable dyes and to block reactive groups. Thus, for example, reactive aldehyde groups are partially inactivated by acetal formation.

b) Methanolic hydrolysis for coarse setting of the molecular weight with a 20-40%, preferably 30% methanolic suspension of the starch with 1% HCl, the latter being held for 2-4 h, preferably 3 h, at 30°-50° C., preferably 40° C. The end of the reaction is achieved by neutralization with 1 N NaOH and subsequent cooling to room temperature. Thereafter the suspension is washed free of chloride.

c) Alkali wash for protein extraction, a 30-50%, preferably 40% suspension in 0.1 N NaOH being prepared and this being held 1-3 h, preferably 2 h, at 30°-50° C., preferably 40° C. Thereafter the procedure is repeated at room temperature.

d) Hydroxyethylation with a hydroxyethylating agent, for example ethylene oxide, and in a particularly preferred embodiment, 2-chloroethanol, the molar ratio of pretruded starch to hydroxyethylating agent being adapted to the desired substitution degree. The starch is dissolved under nitrogen in 20-40%, preferably 30% suspension, in 1 N NaOH for 2 h at 30°-50° C., preferably 40° C. Within 6-10 hrs., preferably 7-8 hrs., the hydroxyethylating agent is added in drops at room temperature, the addition of 10 N NaOH preventing the pH value dropping below 12. Thereafter, this is neutralized with 10% HCl.

e) The solution is heated to 40°-70° C., preferably 60° C., mixed with 0.2% HCl and the hydrolysis followed viscosimetrically. The reaction is terminated by neutralization with NaOH and cooling to room temperature.

f) Purification by filtration through a depth filter and ultrafiltration through a hollow fibre module with a separating limit of about 30,000 Dalton.

g) Spray drying of the end products in a manner known per se.

The hydroxyethyl starches according to the invention are also suitable as carbohydrate components in enteral nutrition of diabetics because the same considerations apply as regards the degradability.

The invention will be explained in detail hereinafter with the aid of an example.

500 g wax maize starch is suspended in a litre of dry methanol and brought to boil. After cooling the methanol is sucked off and the starch washed with water. The washing operation is repeated once.

The starch with a residual moisture content of 28.13% is hydrolyzed in 30% methanolic suspension with 1% HCl for three hours at 40° C. The reaction is stopped by neutralization with 1 N NaOH in methanol and cooling to room temperature. After extraction the starch exhibits a residual moisture content of 16.12% and a mean molecular weight of 900,000.

The starch is suspended in a litre H<sub>2</sub>O, extracted and washed free of chloride. After suction drying the starch has a residual moisture content of 51.29%.

The starch is thereafter stirred in 40% suspension in 0.1 N NaOH for 2 hours at 40° C., again cooled to room temperature and dried by exhaustion (residual moisture content 48.60%). The operation is repeated once at room temperature.

418.0 g (2.58 Mol) of pretreated starch are dissolved in 30% suspension in 1 N NaOH at 40° C. under nitro-

gen. Within 7-8 hrs., 51.9 ml (0.77 Mol) 2-chloroethanol is dripped in. By adding NaOH reduction of the pH value below 12 is avoided. Thereafter, neutralization is carried out with 10% HCl.

The solution is filtered after 1:1 dilution with water via a depth filter (Seitz T750).

The solution is thereafter heated to 60° C., set with 25% HCl to an HCl concentration of 0.2 and hydrolyzed for 4 hours.

The solution is neutralized by addition of sodium hydroxide to pH 6.0 and cooled to room temperature. Thereafter, filtration is carried out via a Seitz EKS filter.

The clear solution is now ultrafiltrated via a hollow fibre module with a separation limit of about 30,000 Dalton and the remaining retentate spray dried.

A hydroxyethyl starch is obtained having a mean molecular weight of 234,000 and a molar substitution degree of 0.26. The C2/C6 ratio is 9.34. The hydroxyethyl starch prepared in this manner has the following substitution pattern (area percentages) which can be determined by complete hydrolysis of HES and subsequent determination of glucose and its hydroxyethyl derivatives via trimethyl silylation:

|                               |        |  |
|-------------------------------|--------|--|
| glucose:                      | 81.42% |  |
| 2-O-hydroxyethyl glucose:     | 12.42% |  |
| 3-O-hydroxyethyl glucose:     | 2.70%  |  |
| 6-O-hydroxyethyl glucose:     | 1.33%  |  |
| 2,2-O-dihydroxyethyl glucose: | 0.21%  |  |
| 2,3-O-dihydroxyethyl glucose: | 0.51%  |  |
| 2,6-O-dihydroxyethyl glucose: | 0.17%  |  |
| 3,3-O-dihydroxyethyl glucose: | 0.10%  |  |
| 3,6-O-dihydroxyethyl glucose: | 0.05%  |  |

We claim:

1. Hydroxyethyl starch for use as plasma expander obtainable by hydrolytic pre-degradation of a starch rich in amylopectin, partial hydroxyethylation up to a certain substitution degree in the presence of alkali and subsequent hydrolytic degradation to a certain molecular weight, characterized in that

it has a mean molecular weight of 60,000-600,000 and a substitution degree MS of 0.15 to 0.5,

the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and

the substitution degree DS lies in the range from 0.15 to 0.5.

2. Hydroxyethyl starch according to claim 1, characterized in that it has a mean molecular weight of 80,000 to 400,000 and a substitution degree MS of 0.2-0.4, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.15 to 0.40.

3. Hydroxyethyl starch according to claim 1, characterized in that it has a mean molecular weight of 100,000 to 300,000 and a substitution degree MS of 0.25-0.35, the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.2 to 0.35.

4. A hydroxyethyl starch for use as plasma expander characterized in that

it has a mean molecular weight of 60,000-600,000 and a substitution degree MS of 0.15 to 0.5,

the ratio of the substitution of C2 to the substitution of C6 of the anhydroglucose units is 8-20 and the substitution degree DS lies in the range from 0.15 to 0.5, produced by a process wherein:

a) starch having a content of amylopectin of >95% is pre-extracted with methanol,

b) the starch is brought by acid hydrolysis to a suitable mean molecular weight,

c) the starch is subjected to an alkali wash,

d) the starch is hydroxyethylated by means of a hydroxyethylation agent under alkaline conditions,

e) the molecular weight is exactly set by acid hydrolysis,

f) the hydroxyethyl starch thus obtained is pulled, and

g) spray dried,

characterized in that the hydroxyethylation agent used is selected from the group consisting of 2-chloroethanol and ethylene oxide and the hydroxyethylation is carried out under alkaline conditions at room temperature.

5. A starch of claim 4 characterized in that the pH value is kept at a value of about 12 during the hydroxyethylation.

6. A starch of claim 4 characterized in that the temperature is kept at a value of about 20° to 25° C.

7. A starch of claim 4 characterized in that the hydroxyethyl starch is purified by filtration and ultrafiltration.

• • • • •



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ISTMT

DATE PRINTED  
02/05/2008

OMRI M. BEHR, ESQ.  
325 PIERSON AVENUE  
EDISON NJ 08837

## MAINTENANCE FEE STATEMENT

According to the records of the U.S. Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450.

| PATENT<br>NUMBER | FEE AMT    | SUR<br>CHARGE | PYMT<br>DATE | U.S.<br>APPLICATION<br>NUMBER | PATENT<br>ISSUE<br>DATE | APPL.<br>FILING<br>DATE | PAYMENT<br>YEAR | SMALL<br>ENTITY? | ATTY DKT<br>NUMBER |
|------------------|------------|---------------|--------------|-------------------------------|-------------------------|-------------------------|-----------------|------------------|--------------------|
| 5,218,108        | \$3,320.00 | \$0.00        | 11/24/04     | 07/533,294                    | 06/08/93                | 06/05/90                | 12              | NO               | LUDR3.0-036        |



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| PATENT<br>NUMBER | FEE AMT    | SUR<br>CHARGE | PYMT<br>DATE | U.S.<br>APPLICATION<br>NUMBER | PATENT<br>ISSUE<br>DATE | APPL.<br>FILING<br>DATE | PAYMENT<br>YEAR | SMALL<br>ENTITY? | ATTY DKT<br>NUMBER |
|------------------|------------|---------------|--------------|-------------------------------|-------------------------|-------------------------|-----------------|------------------|--------------------|
| 5,218,108        | \$1,950.00 | \$0.00        | 11/13/00     | 07/533,294                    | 06/08/93                | 06/05/90                | 08              | NO               | LUDR3.0-036        |



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|------------------|------------|---------------|--------------|-------------------------------|-------------------------|-------------------------|-----------------|------------------|--------------------|
| 5,218,108        | \$1,020.00 | \$0.00        | 11/25/96     | 07/533,294                    | 06/08/93                | 06/05/90                | 04              | NO               | LUDR3.0-036        |



Fresenius  
Kabi

### **Voluven 6 % Solution for Infusion**

Listing of the actual registrations within EU and Non-EU countries

| <b>Country</b>                    | <b>Reg-Date</b> | <b>Reg-No.</b> |
|-----------------------------------|-----------------|----------------|
| Germany<br>(Voluven)              | 22-Jun-1999     | 42093.00.00    |
| Germany<br>(Voluven<br>Fresenius) | 26-Aug-1999     | 45010.00.00    |
| Germany<br>(Voluven 6%)           | 26-Aug-1999     | 44943.00.00    |

Registrations based on the German marketing authorisation no. 42093.00.00

| <b>Country</b> | <b>Reg-Date</b> | <b>Reg-No.</b> |
|----------------|-----------------|----------------|
| Switzerland    | 27-Jun-2000     | 55093          |



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Food and Drug Administration  
1401 Rockville Pike  
Rockville MD 20852-1448

Our Reference: BB-IND 9740

April 5, 2001

Fresenius Kabi Deutschland, GmbH  
Attention: Rosemary P. Davis  
Manager Of Regulatory Affairs  
P.O. Box 597  
8484 US 70 West  
Clayton, NC 27520-0597



Dear Ms. Davis:

The Center for Biologics Evaluation and Research has received your **Investigational New Drug Application (IND)**. The following product name and BB-IND number have been assigned to this application. They serve only to identify it and do not imply that this Center either endorses or does not endorse your application.

BB-IND #: 9740

SPONSOR: **Fresenius Kabi Deutschland, GmbH**

PRODUCT NAME: **High Molecular Weight Hydroxyethyl Starch - 6% (Voluven)**

DATE OF SUBMISSION: **March 23, 2001**

DATE OF RECEIPT: **March 26, 2001**

This BB-IND number should be used to identify all future correspondence and submissions, as well as telephone inquiries concerning this IND. Please provide an **original and two copies of every submission to this file**. Please include three originals of all illustrations which do not reproduce well.

It is understood that studies in humans will not be initiated until 30 days after the date of receipt shown above. If this office notifies you, verbally or in writing, of serious deficiencies that require correction before human studies can begin, it is understood that you will continue to withhold such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory. If such a clinical hold is placed on this file, you will be notified in writing of the reasons for placing the IND on hold.

You are responsible for compliance with applicable portions of the Public Health Service Act, the Federal Food, Drug, and Cosmetic Act, and the Code of Federal Regulations (CFR). A copy of 21 CFR Part 312, pertaining to INDs, is enclosed. Copies of other pertinent regulations are

Page 2 - BB-IND 9740

available from this Center upon request. The following points regarding obligations of an IND sponsor are included for your information only, and are not intended to be comprehensive.

Progress reports are required at intervals not exceeding one year and are due within 60 days of the anniversary of the date that the IND went into effect. Any unexpected, fatal or immediately life-threatening reaction which is associated with use of this product must be reported to this Center within three working days, and all serious, unexpected adverse experiences must be reported, in writing, to this Center and to all study centers within ten working days.

Charging for an investigational product in a clinical trial under an IND is not permitted without the prior written approval of the FDA.

Prior to use of each new lot of the investigational biologic in clinical trials, please submit the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results).

If not included in your submission, please provide copies of the consent forms for each clinical study. A copy of the requirements for and elements of informed consent are enclosed. Also, please provide documentation of the institutional review board approval(s) for each clinical study.

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR Part 58, copies available upon request). If such studies have not been conducted in compliance with these regulations, please provide a statement describing in detail all differences between the practices used and those required in the regulations.

Item 7a of form FDA 1571 requests that either an "environmental assessment," or a "claim for categorical exclusion" from the requirements for environmental assessment, be included in the IND. If you did not include a response to this item with your application, please submit one. See the enclosed information sheet for additional information on how these requirements may be addressed.

Sponsors of INDs for products used to treat life-threatening or severely debilitating diseases are encouraged to consider the interim rule outlined in 21 CFR 312.80 through 312.88.

Telephone inquiries concerning this IND should be made directly to me at (301) 827-3524.

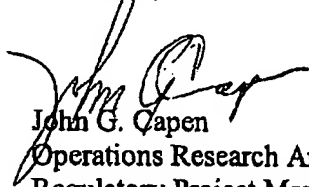
Correspondence regarding this file should be addressed as follows:

Center for Biologics Evaluation and Research  
ATTN: Office of Blood Research and Review  
HFM 99, Room 200N  
1401 Rockville Pike  
Rockville, MD 20852-1448

Page 3 - BB-IND 9740

If we have any comments after we have reviewed this submission, we will contact you.

Sincerely yours,



John G. Capen

Operations Research Analyst  
Regulatory Project Management Branch  
Division of Blood Applications  
Office of Blood Research and Review  
Center for Biologics Evaluation and Research

Enclosures (3):

21 CFR Part 312  
21 CFR 50.20, 50.25  
Information sheet on 21 CFR 25.24

***Regulatory Correspondence/Contacts Log***

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**2000**

**August 29, 2000**

**PRE-IND MEETING**

Clinical study design was discussed in detail and the FDA provided a number of specific recommendations on study design and size as well as on endpoints and other documentation to be captured in the study.

**2001**

**March 23, 2001**

**SUBMISSION OF IND (BB-IND 9740)**

**April 5, 2001**

**FDA ACKNOWLEDGES RECEIPT OF IND**

**May 30, 2001**

**RECEIPT OF FDA QUESTIONS AND REQUEST  
FOR PROTOCOL AMENDMENT**

**July 6, 2001**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 001)**

Response to FDA letter dated May 30, 2001

**September 2001**

**START OF PHASE III STUDY HS-13-30-US**

**August 2, 2001**

**SUBMISSION OF INFORMATION AMENDMENT  
(Serial No. 002)**

Submission of documentation for a compatibility study

***Regulatory Correspondence/Contacts Log***

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**2002**

**January 17, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 003)**

Submission of positive votes and final informed consent form for all centers

**May 8, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 004)**

**June 25, 2002**

Change in protocol  
**SUBMISSION OF ANNUAL REPORT  
(Serial No. 005)**

**July 17, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 006)**

Protocol signature of 2 new principal investigators

**September 16, 2002**

**FDA LETTER RECEIVED**

Questions and comments on IND submission dated May 8, 2002  
(Serial No. 004) obtained

**October 7, 2002**

**SUBMISSION OF RESPONSE TO FDA LETTER  
DATED SEPTEMBER 16, 2002  
(Serial No. 007)**

**December 16, 2002**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 008)**

Closing of a study center etc.

**2003**

**May 8, 2003**

**SUBMISSION OF PROTOCOL AMENDMENT  
(Serial No. 009)**

***Regulatory Correspondence/Contacts Log***

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Inclusion of additional subinvestigator etc.

**July 1, 2003**

**SUBMISSION OF INFORMATION AMENDMENT  
(Serial No. 010)**

Submission of documentation for a compatibility study

**July 22, 2003**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 011)**

**2004**

**June 24, 2004**

**REQUEST FOR PRE-NDA TYPE B MEETING  
(Serial No. 012)**

**July 5, 2005**

**SUBMISSION OF ANNUAL REPORT  
(Serial No. 013)**

**July 28, 2004**

**REQUEST FOR PRE-NDA TYPE B MEETING  
(Serial No. 014)**

**September 1, 2004**

**PRE-NDA MEETING WITH FDA**

Requested Pre-NDA Type B Meeting held with FDA

**October 19, 2004**

**SUBMISSION OF GENERAL CORRESPONDENCE  
(Serial No. 015)**

Designation of domestic agent

**October 20, 2004**

**SUBMISSION OF GENERAL CORRESPONDENCE  
(Serial No. 016)**

Study termination in all centers

**2005**

**SUBMISSION OF ANNUAL REPORT**  
(Serial No. 017)

**SUBMISSION OF GENERAL CORRESPONDENCE**  
(Serial No. 018)

**SUBMISSION OF ANNUAL REPORT**  
(Serial No. 019)

**SUBMISSION OF ANNUAL REPORT**  
(Serial No. 020)

***Regulatory Correspondence/Contacts Log***

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**2007****February 28, 2007****SUBMISSION ORIGINAL NDA**

Submission of original NDA

**March 23, 2007****CORRESPONDENCE FROM FDA**

FDA acknowledges receipt of NDA on March 1, 2007

**March 30, 2007****TELECON FROM FDA**

FDA request additional copy of Module 3 and Methods Validation Package

**March 30, 2007****SUBMISSION NDA COPIES**

Submission of requested copy of Module 3 and Methods Validation Package

**April 30, 2007****CORRESPONDENCE FROM FDA**

FDA advises that NDA is filed.

**June 11, 2007****TELECON FROM FDA**

FDA requested teleconference.

**June 11, 2007****FAX FROM FDA INFORMATION REQUEST**

FDA sends fax to list questions of FDA reviewers.

**June 12, 2007****TELECONS TO/FROM FDA**

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*Regulatory Correspondence/Contacts Log*

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|---------------|--|-------------------------|
| June 13, 2007 | TELECON TO FDA   |                         |
| June 13, 2007 | EMAIL FROM FDA   |                         |
| June 13, 2007 | EMAIL TO FDA   |                         |
| June 18, 2007 | TELECONFERENCE WITH FDA  |                         |
| June 18, 2007 | EMAIL TO FDA   |                         |
| June 18, 2007 | EMAIL FROM FDA   |                         |
| June 25, 2007 | SUBMISSION   | NDA AMENDMENT           |
|               | Submission of response to FDA questions.                               |                         |
| June 26, 2007 | SUBMISSION   | SAFETY UPDATE<br>REPORT |
|               | Submission of first safety update report.<br>(Seven volume submission) |                         |
| June 28, 2007 | EMAIL TO FDA   |                         |
| June 29, 2007 | EMAIL FROM FDA   |                         |
| July 18, 2007 | FAX FROM FDA   | INFORMATION<br>REQUEST  |

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**Regulatory Correspondence/Contacts Log**

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|--------------------------|---|----------------------------|
| <b>July 26, 2007</b>     | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>       |
|                          | Submission of response to FDA questions presented in fax of July 18.                      |                            |
| <b>July 30, 2007</b>     | <b>FAX FROM FDA</b>   | <b>INFORMATION REQUEST</b> |
|                          | FDA sends fax to request information on CMC and clinical matters.                         |                            |
| <b>August 6, 2007</b>    | <b>TELECON TO FDA</b>   | <b>INFORMATION REQUEST</b> |
| <b>August 16, 2007</b>   | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>       |
|                          | Submission of response to FDA questions presented in fax of July 30.                      |                            |
| <b>August 17, 2007</b>   | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>       |
|                          | Submission of draft Summary Basis of Approval as requested by FDA in telecon of August 6. |                            |
| <b>August 21, 2007</b>   | <b>TELECON TO FDA</b>   | <b>ADMINISTRATIVE</b>      |
| <b>August 21, 2007</b>   | <b>EMAIL TO FDA</b>   | <b>ADMINISTRATIVE</b>      |
| <b>August 22, 2007</b>   | <b>EMAIL TO FDA</b>   | <b>ADMINISTRATIVE</b>      |
| <b>September 4, 2007</b> | <b>FAX FROM FDA</b>   | <b>INFORMATION REQUEST</b> |

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|-----------------------|---|--------------------------|
| September 6, 2007     | SUBMISSION  | NDA AMENDMENT            |
|                       | Submission of information in response to FDA fax of September 4, 2007.                            |                          |
| September 13, 2007    | FAX FROM FDA  | INFORMATION REQUEST      |
| September 19/20, 2007 | TELECONS FROM FDA   | INFORMATION REQUEST      |
| September 20, 2007    | SUBMISSION  | NDA AMENDMENT            |
|                       | Submission of information in response to FDA fax of September 13, 2007.                           |                          |
| September 20, 2007    | EMAIL FROM FDA  | INFORMATION REQUEST - PI |
| September 25, 2007    | TELECON TO FDA  | INFORMATION REQUEST      |
| October 1, 2007       | TELECON FROM FDA  | INFORMATION REQUEST      |
| October 2, 2007       | TELECON TO FDA  | INFORMATION REQUEST      |
| October 2, 2007       | SUBMISSION  | NDA AMENDMENT            |
|                       | Submission of information in response to FDA email of September 20, 2007 requesting PI revisions. |                          |

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**Regulatory Correspondence/Contacts Log**

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| October 4, 2007    | SUBMISSION   | NDA AMENDMENT               |
|                    | Submission of information in response to FDA telecom of October 1, 2007 asking that request for approval of proprietary name be submitted. |                             |
| October 5, 2007    | TELECON/EMAIL<br>FROM FDA  | INFORMATION<br>REQUEST - PI |
| October 9/10, 2007 | TELECON TO FDA   | INFORMATION<br>REQUEST      |
| October 11, 2007   | EMAIL TO FDA   | INFORMATION<br>REQUEST      |
| October 12, 2007   | SUBMISSION   | NDA AMENDMENT               |
|                    | Submission of information in response to FDA email of October 5, 2007 requesting further PI revisions.                                     |                             |
| October 16, 2007   | TELECON FROM FDA   | TELECONFERENCE<br>REQUEST   |
| October 17, 2007   | TELECON TO FDA   | TELECONFERENCE<br>REQUEST   |
| October 17, 2007   | EMAIL TO FDA   | TELECONFERENCE<br>REQUEST   |
| October 17, 2007   | SUBMISSION   | NDA AMENDMENT               |
| October 18, 2007   | TELECON FROM FDA   | TELECONFERENCE<br>REQUEST   |
| October 22, 2007   | EMAIL TO FDA   | TELECONFERENCE<br>REQUEST   |

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**Regulatory Correspondence/Contacts Log**

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|------------------|----------------------------|---------------------------|
| October 23, 2007 | TELECON FROM FDA           | TELECONFERENCE<br>REQUEST |
| October 30, 2007 | EMAIL TO FDA               | TELECONFERENCE<br>REQUEST |
| October 31, 2007 | TELECONFERENCE<br>WITH FDA |                           |
| October 31, 2007 | TELECON FROM FDA           | ADMINISTRATIVE            |
| October 31, 2007 | EMAIL FROM FDA             | ADMINISTRATIVE            |
| November 2, 2007 | TELECON FROM FDA           | CLINICAL                  |
| November 6, 2007 | TELECON TO FDA             | CLINICAL                  |
| November 8, 2007 | TELECON TO FDA             | CLINICAL                  |
| November 8, 2007 | EMAIL TO FDA               | CLINICAL                  |
| November 9, 2007 | SUBMISSION                 | NDA AMENDMENT             |

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|-------------------|--------------------------|-----------------------------|
| November 9, 2007  | TELECONS FROM/<br>TO FDA | CLINICAL                    |
| November 9, 2007  | FAX TO FDA               | CLINICAL                    |
| November 9, 2007  | EMAIL/FAX<br>FROM FDA    | INFORMATION<br>REQUEST - PI |
| November 13, 2007 | EMAIL TO FDA             | CLINICAL                    |
| November 13, 2007 | TELECON TO FDA           | PI REVISIONS                |
| November 14, 2007 | SUBMISSION               | NDA AMENDMENT               |
| November 16, 2007 | SUBMISSION               | NDA AMENDMENT               |
| November 26, 2007 | SUBMISSION               | NDA AMENDMENT               |
| November 28, 2007 | TELECON FROM FDA         | PI REVISIONS                |
| November 28, 2007 | EMAIL TO FDA             | PI REVISIONS                |
| November 29, 2007 | EMAIL FROM FDA           | PI REVISIONS/<br>CLINICAL   |
| November 29, 2007 | TELECONS TO FDA          | PI REVISIONS/<br>CLINICAL   |

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**Regulatory Correspondence/Contacts Log**

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| <b>November 29/30, 2007</b> | <b>EMAILS TO/FROM FDA</b>              | <b>PI REVISIONS/<br/>CLINICAL</b>   |
| <b>November 30, 2007</b>    | <b>TELECONS/EMAILS<br/>TO/FROM FDA</b> | <b>PEDIATRIC STUDIES</b>  |
| <b>December 3, 2007</b>     | <b>SUBMISSION</b>                      | <b>NDA AMENDMENT</b><br><br>Submission of additional pediatric information as requested by FDA on November 30, 2007.  |
| <b>December 4, 2007</b>     | <b>EMAIL TO FDA</b>                    | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 5, 2007</b>     | <b>TELECON FROM FDA</b>                | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 5, 2007</b>     | <b>EMAIL TO FDA</b>                    | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 5, 2007</b>     | <b>SUBMISSION</b>                      | <b>NDA AMENDMENT</b><br><br>Submission of amendment containing PI revisions and information on PM study/commitment as requested by FDA on November 28-30, 2007. |
| <b>December 7, 2007</b>     | <b>TELECONS TO/FROM<br/>FDA</b>        | <b>PI REVISIONS<br/>PM STUDY</b>  |
| <b>December 10, 2007</b>    | <b>TELECONS TO FDA</b>                 | <b>PI REVISIONS<br/>PM STUDY</b>  |

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**Regulatory Correspondence/Contacts Log**

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| <b>December 10, 2007</b>    | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>               |
|                             | Submission of amendment containing PI revisions requested by FDA on December 7, 2007 and PM commitment.                 |                                    |
| <b>December 10, 2007</b>    | <b>CORRESPONDENCE FROM FDA</b>  | <b>PROPRIETARY NAME ACCEPTANCE</b> |
|                             | FDA forwards letter stating that proprietary name is acceptable. A fax copy of the letter is sent on December 11, 2007. |                                    |
| <b>December 11-12, 2007</b> | <b>EMAIL TO FDA</b>   | <b>PI REVISIONS PM STUDY</b>       |
| <b>December 12/13, 2007</b> | <b>TELECON/EMAIL FROM FDA</b>   | <b>PI REVISIONS PM STUDY</b>       |
| <b>December 14, 2007</b>    | <b>TELECON FROM FDA</b>   | <b>PEDIATRIC DATA</b>              |
| <b>December 17, 2007</b>    | <b>EMAIL TO FDA</b>   | <b>PEDIATRIC DATA</b>              |
| <b>December 17, 2007</b>    | <b>TELECONFERENCE WITH FDA</b>  | <b>PEDIATRIC DATA</b>              |
| <b>December 18, 2007</b>    | <b>TELECON TO FDA</b>   | <b>PEDIATRIC DATA</b>              |
| <b>December 18, 2007</b>    | <b>SUBMISSION</b>   | <b>NDA AMENDMENT</b>               |
|                             | Submission of amendment containing proposal for pediatric study, commitment wording and PI revisions.                   |                                    |
| <b>December 19, 2007</b>    | <b>TELECON TO FDA</b>   | <b>PEDIATRIC DATA</b>              |

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| <b>December 20, 2007</b> | <b>TELECON/EMAIL<br/>TO/FROM FDA</b> | <b>PEDIATRIC DATA</b> |
| <b>December 27, 2007</b> | <b>FAX/TELECON<br/>FROM FDA</b>      | <b>NDA APPROVAL</b>   |
| <b>December 27, 2007</b> | <b>CORRESPONDENCE<br/>FROM FDA</b>   | <b>NDA APPROVAL</b>   |

NDA approval letter (postmarked December 31, 2007; received January 2, 2008)